UNIVERSITY OF ALBERTA

THE EFFICACY OF MANUAL LYMPH DRAINAGE IN REDUCTION OF ARM VOLUME IN WOMEN TREATED WITH MULTI-LAYERED COMPRESSION BANDAGING FOR BREAST CANCER RELATED LYMPHEDEMA

BY

MARGARET LYNN McNEELY ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE.**

DEPARTMENT OF PHYSICAL THERAPY

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **THE EFFICACY OF MANUAL LYMPH DRAINAGE IN REDUCTION OF ARM VOLUME IN WOMEN TREATED WITH MULTI-LAYERED COMPRESSION BANDAGING FOR BREAST CANCER RELATED LYMPHEDEMA** submitted by **MARGARET LYNN McNEELY** in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE.**

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ABSTRACT

The study was a randomized, controlled treatment study to determine the efficacy of manual lymph drainage (MLD) in the reduction of arm volume in women receiving multi-layered compression bandaging (CB) for breast cancer related lymphedema. Fifty women were randomly assigned to receive either MLD in combination with CB or CB alone. Independent assessors, blinded to subject treatment assignment, administered the outcome measurements. Both water displacement volumetry and circumference measurements were used to assess lymphedema volume. Forty-five subjects completed the study. No statistically significant difference was found between the groups for overall lymphedema reduction or in the rate of reduction. These findings indicate that CB, with or without MLD, is an effective intervention in reducing arm lymphedema volume. There may be an additional benefit from the application of MLD for women with mild lymphedema; however, this finding will need to be further examined in the research setting.

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DEDICATION

I would like to dedicate this work to my grandmother, Mrs. Frances Reed. Thank you for all the love and support you have given and continue to give to me. You have provided me with the foundation of integrity and hard work, and have shown me the importance of truly caring for others. Your endless energy, positive perspective and fearlessness in dealing with life's changes and challenges have provided me with the motivation to complete this work.

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I: CHAPTER ONE

INTRODUCTION

I-1. INTRODUCTION:

Breast cancer remains the most frequently occurring form of cancer in North American women (1). The lifetime risk for breast cancer in Canadian women is 1 in 9.5 (1). The Canadian Cancer Society estimate for the number of new cases of breast cancer in 2001 was 19,500 (1). In Alberta, the estimate for new breast cancer cases in 2001 was 1,700 (1). Currently, the estimated relative five-year survival rate for breast cancer is 86% (2). Consequently, as many women are affected by, and survive breast cancer, there is a need to attend to the physical and emotional effects of this cancer and its treatment. A major complication of breast cancer is lymphedema, a swelling that occurs as a result of an accumulation of lymphatic fluid (3). Disruption of lymphatic pathways in the upper limb, especially deep lymph-collectors, which causes this swelling in breast cancer patients, may be the result of tumour blockage, axillary dissection, and/or radiation therapy (3,4). The leading symptom is usually a painless but significant swelling of the arm on the surgical side (4).

Studies on the incidence of breast cancer related lymphedema are well represented in the literature; however, there is considerable variance in their findings (5,6,7). For instance, recent studies have indicated the incidence of lymphedema in breast cancer patients to range is as low as 1-3 % in patients undergoing sentinel lymphadenectomy (8) to as high as 60% in patients treated with modified radical mastectomy, axillary dissection and high dose radiation therapy (9). The variance in the reported incidence of lymphedema is related to treatment factors and also due, in part, to the lack of consistency in defining "clinically significant lymphedema", as well as to variations in the measurement techniques used and in the length of patient follow-up (10). Despite improvements in surgical and radiotherapeutic techniques, the incidence of breast cancer related lymphedema is about 20% (11).

Following primary therapies for breast cancer, lymphedema may present immediately after breast surgery, or following a latent period of months or even years (12,13). Though the majority of lymphedema cases are reported to develop within 1 year following breast cancer treatment (14), lymphedema onset has been documented to occur as late as 30 years from initial treatment (15). The swelling may be mild to severe, and, if left untreated, lymphedema has been found to have a significant tendency to increase with time, both in the volume of edema and in stage of tissue fibrosis (16).

Functionally, the distended tissues and the increased weight of the limb may result in impairment of upper extremity range of motion. This impairment has important clinical implications because such difficulties in function influence the home and work environment. The impaired range of motion at the shoulder causes difficulty in simple tasks such as washing the hair, putting on clothing and reaching for objects overhead (17). Clinical experience reveals that, in severe cases, women often complain that there is a loss of power in the arm and that it is easily fatigued with use. In addition, research has demonstrated significant psychosocial morbidity (17,18,19), and poorer quality of life in women with lymphedema (20). For example, pain has been reported in approximately 30% of lymphedema patients (13), and has been associated with higher psychosocial impairment (21). Recurrent infections in the limb can also become a significant problem (22), and a rare, but fatal, complication of chronic lymphedema is another form of cancer called lymphangiosarcoma (23,24). Clearly, early and appropriate treatment of lymphedema is necessary to prevent further complications and increased disability.

I-2. STATEMENT OF THE PROBLEM:

At present, there is no known intervention to cure lymphedema. Therapeutic interventions for lymphedema are prescribed to reduce pain and swelling, restore limb function, improve cosmesis, and minimize the risk of infection in the limb. While progress in surgical techniques offers hope, conservative treatment remains the treatment of choice, with physical therapy being the most common treatment method used. Unfortunately, there is a paucity of research in this area and conservative treatment for lymphedema is not standardized. Controversies exist concerning the different therapeutic approaches with personal preferences based on experience often overriding and preceding experimental fact. For example, there are numerous physical therapy interventions that are potentially effective in treating lymphedema including various compression therapies, massage techniques, electrophysical agents, exercise, and education. Consequently, treatment varies depending on where the patient lives, the resources available, and the expertise of the involved healthcare professional. Most of the data available on various treatment approaches have been obtained by means of retrospective analysis, and most therapies currently prescribed are based on subjective clinical experience rather than objective scientific data (10,13).

A combined treatment program called Complex Physical Therapy (CPT), also known as Complex Decongestive Physiotherapy (CDP) or Complex Lymphedema Therapy (CLT), has been gaining popularity in North America. CPT consists of education (specifically with an emphasis on meticulous skin care), manual lymph drainage massage, multi-layered compression bandaging and a specialized exercise program*. Previous case reports reveal impressive reductions in lymphedema following CPT treatment with return of the limb to a normal or near normal state (25,26,27). The reported average lymphedema volume reduction from CPT is approximately 50% (28,29). The central treatment of this program is manual lymph drainage (MLD), a costly, labour-intensive, specialized massage technique. It is unclear, however, whether the reductions in lymphedema from this program are mainly due to the MLD or to the less costly components such as multi-layered compression bandaging (CB) and exercise. Early evidence has suggested that the CB may be primarily responsible for the reductions achieved by this combined technique (30,31). The continuing focus on rising health care costs and fiscal restraint has resulted in a need for cost-effective intervention programs. The relatively high cost of MLD, as compared to bandaging alone, has provided added impetus to evaluate the potential benefit of the individual components of CPT to determine their efficiency and effectiveness.

---

* Information on this program may be obtained from the Lymphoedema Association of Australia, University of Adelaide, Box 498 G.P.O., Adelaide, S.A. 5001, Australia.

The purpose of this study was to compare the reduction in arm lymphedema volume achieved from MLD in combination with CB to that achieved by CB alone. The study was designed to assess the efficacy of MLD in combination with CB and to determine whether or not it is significantly better than the less costly treatment of CB alone.

I-3. HYPOTHESES:

The purpose of this study was to test the following hypotheses:

1. If subjects receive MLD in combination with CB, then there will be a significant reduction in the volume of lymphedema in the affected limb.
2. If subjects receive CB alone, then there will be a significant reduction in the volume of lymphedema in the affected limb.
3. When MLD and CB are combined, then there will be a significantly larger reduction in lymphedema volume in the affected limb when compared to the reduction from CB alone.
4. When MLD and CB are combined, then there will be a significant greater rate of reduction in lymphedema volume when compared to the group receiving CB alone.
5. There will be a significantly high correlation ($r > 0.80$) between water displacement volumetry and the volume calculated from circumference measurements (concurrent validity).

I-4. DEFINITIONS:

1. Affected limb: The lymphedematous arm on the ipsilateral side of the breast surgery.

2. Unaffected limb: The contralateral, normal arm (no evidence of lymphedema).

3. Lymphedema volume: The difference between the volume of the affected and unaffected arms. The difference was determined by volumetry and was expressed in millilitres (mL).

4. Percent volume increase in the affected arm: The percent volume increase of the lymphedematous arm will be determined by dividing the affected arm volume by the unaffected arm volume, and subtracting one and multiplying the result by one hundred.

5. Mild lymphedema: For the purposes of the present study, mild lymphedema was considered a percent volume increase in the lymphedematous arm of less than 16 percent (Further details provided in Chapter III-7-c).

6. Moderate lymphedema: For the purposes of the present study, moderate lymphedema was considered a percent volume increase in the lymphedematous arm from 16 percent to 37.5 percent (Further details provided in Chapter III-7-c.).

7. Severe Lymphedema: For the purpose of the present study, severe lymphedema was considered a percent volume increase in the lymphedematous arm of greater than 37.5 percent (Further details provided in Chapter III-7-c).

8. Manual Lymph Drainage (MLD): A specialized massage technique that stimulates lymph flow and attempts to access collateral lymphatics to drain fluid from impaired regions to regions of normal lymphatic function.

9. The Vodder Method of MLD: The Vodder Method (Appendix A) of manual lymph drainage was used in this trial. The Vodder Method is the original method of MLD and was developed by Dr. Emil Vodder as a specific technique for the treatment of lymphedema (32). The Vodder Method is instructed to health professionals over four weeklong courses. Certification in the technique requires successful completion of oral, written and practical examinations.

10. Multi-layered Compression Bandaging (CB): A bandaging technique that applies gradient pressure to the limb. Bandaging always starts at the distal end of the arm and then continues proximally. The pressure applied is greatest at the distal end of the limb and is achieved by applying more layers distally than proximally (Appendix B).

11. Water Displacement Volumetry (volumetry): This measurement technique uses the principle of water displacement. The limb is immersed in a water tank and the overflow is collected and measured.

12. Measurement of Circumference (circumference measurements): The circumference of the limb is measured at predetermined locations along the arm using a standard tape measure (Section III-6-d-ii). This is also known as girth measurements.

I-5. LIMITATIONS:

The data collected was limited to unilateral arm lymphedema due to breast cancer treatment. The results were limited by the validity and reliability of the measurement methods in determining lymphedema volume, and by the reliability of the Independent Assessor (IA) performing the measurements. The study was designed to determine the effect of treatment on lymphedema volume and the results provided information regarding the effect of treatment for a one-month period. Duration of treatment effect was not examined in this study as the ability to maintain the treatment reduction is affected by the extent of the damage to the lymphatic system, and highly dependent on patient adherence to the maintenance program.

I-6. DELIMITATIONS OF THE STUDY:

The delimitations of the study were as follows:

1. This study examined breast cancer treatment related lymphedema of the arm and therefore conclusions regarding lymphedema due to cancer recurrence, or other types and locations of lymphedema cannot be made.
2. This study compared the results from two treatment components of Complex Physical Therapy, multilayered compression bandaging and manual lymph drainage, therefore comparisons to other treatment techniques or to the complete CPT program cannot be made.

I-7. ETHICAL CONSIDERATIONS:

The present study proposal was presented to, and approved by, the Student Project Research Review Committee in the Department of Physical Therapy (Appendix C).

Consent from the Research Ethics Committee of the Cross Cancer Institute and the Health Research Ethics Board of the University of Alberta was obtained (Appendix D). Information about the study was outlined in a letter of information (Appendix E). Subjects were asked to sign a consent form (Appendix F), which outlined the right to withdraw, confidentiality, and the risks and benefits involved in the study. Non-participation in this study did not affect accessibility to assessment and treatment at the Rehabilitation Department of the Cross Cancer Institute. This study involved the collection of information usually sought as part of the assessment and treatment of breast cancer patients with secondary lymphedema. The risk to the subject in participating in this study was minimal and did not represent an increase from the risk assumed with standard assessment and treatment procedures. The risk to treatment was a small chance of skin reaction (allergy) to the bandages. As well, the bandages were bulky and cumbersome and if applied too tightly could cause aching and/or pain. Subjects were advised to remove the bandaging if pain occurred. Subjects were free to withdraw from the study at any time without prejudice or coercion.

II: CHAPTER TWO

LITERATURE REVIEW

Knowledge of normal lymphatic physiology is important to understand the pathophysiology of lymphedema and the rationale for current therapeutic approaches to lymphedema treatment. Therefore, the literature has been reviewed in six sections: 1.) The Lymphatic System, 2.) Physiology of Lymph Circulation, 3.) Pathophysiology of Lymphedema, 4.) Etiology of Breast Cancer Related Lymphedema, 5.) Overview of Treatment, 6.) Summary.

II-1. THE LYMPHATIC SYSTEM:

The lymphatic system consists of a fluid called lymph, vessels that convey lymph, and lymph nodes, lymphatic nodules, the spleen and the thymus (33). The lymphatic system parallels the vascular system, and is responsible for returning the excess (10-20%) of the tissue fluid formed at the arterial ends of the capillaries back into the blood circulation (33). The lymphatic system is a one-way transport system that has an important role in fluid/macromolecule homeostasis, lipid absorption, and immune function. It accomplishes this role via the generation of a controlled lymph circulation through a series of progressive conduits in the lymphatic system: the lymphatic capillaries, collecting vessels, lymph nodes, trunks and ducts (34). When the interstitial fluid enters the initial lymphatic capillaries, it is then called lymph (35). The lymphatic capillaries are blind-ended sacs, which consist of single-layer endothelial cells with an incomplete

(36) or absent basement membrane (33). The endothelial cells of the smallest lymphatic vessels are just touching, overlapping or interdigitating, rather than fused together as in blood capillaries (37). The overlapped portions of the cells are attached to elastic fibres, which are tethered to the extracellular matrix (ECM) (34). These fibres are called anchoring filaments. Anchoring filaments are sensitive to stress within the interstitial spaces, spread the endothelial cells, and create a small pressure gradient (tissue pump) to allow entry of interstitial fluid and molecules into the lymphatic vessel (34). The overlapping cell-to-cell junctions also likely serve as a 'second valve system' that prevents retrograde flow from the lymphatic capillary to the interstitial spaces (34). From the lymph capillaries, fluid flows to lymphatic precollector vessels, then to the larger collector lymphatics (38). Unlike the initial lymphatics, collecting vessels are not tethered to the ECM but instead contain smooth muscle and one-way valves to aid in lymph propulsion and to prevent retrograde flow (34). Segments of collecting lymphatic vessels between the valves are termed lymphangions. The rhythmic contractility of the smooth muscle of each lymphangion propels lymph through the lymphatic vessel (34). In most cases, collecting lymphatic vessels pass through a series of local lymph nodes (38). Lymph enters the node through several afferent lymphatic vessels and the fluid is filtered as it permeates through channels within the node (33). A vascular compartment accompanies each lymph node compartment for fluid exchange and cell transport (34). Efferent lymph vessels unite to form lymphatic trunks and return the lymph to the venous system. The superficial lymphatics of the skin, which drain the dermal layer and subcutaneous fat, accompany superficial veins (33). The deep lymph channels drain the muscular compartment, joints, and the synovial tissue (33), eventually reaching either the

thoracic duct or the right lymphatic duct, and re-enter the circulatory system by joining the left and right brachiocephalic veins at the base of the neck (33). Several factors are involved in this one-way drainage system that moves the lymph from the tissue spaces to the lymph nodes and then returns the fluid to the venous system (39):

1. Filtration pressure in the interstitial spaces (33).
2. Skeletal muscle contractions or stretching compress the lymphatic vessels, moving lymph in the direction determined by their valves; both active and passive movements increase lymph flow (33, 40).
3. The pulsation of neighbouring arteries, which compress the adjacent lymphatic vessels, assist lymph flow (33, 41).
4. Breathing, especially deep diaphragmatic breathing, and the resulting negative blood pressure in the brachiocephalic veins (into which lymph drains), promotes flow of lymph (33).
5. Smooth muscle in the walls of the lymphatic collectors and trunks is found proximal to their valves, and stimulation of sympathetic nerves accompanying them results in their contraction (41). Lymphatic contractility plays a crucial role in the regulation and generation of lymph transport. Lymph flow velocities fluctuate; increasing flow rates in response to intrinsic forces and to increasing lymphatic vessel diameter (34). Pulsatile contractions in the thoracic duct also occur (41), and, because of the numerous valves along this structure, lymph is forced proximally (unidirectional) by this muscular action (33).
6. Massage increases the rate of lymph flow in normal (42) and edematous limbs (33).

Lymphatic vessels can repair easily and new vessels can regenerate after damage (33). As well, to compensate for injury to the system, lymph fluid can be redirected through collateral circulation, and new routes of flow can be established (43). Since lymphatic vessels anastomose freely and cross the midline of the body (33), drainage to another quadrant is possible.

In addition to its transport functions, the lymphatic system plays a vital role in the body's defense against disease (38). The dissemination of immunological memory and antibodies is dependent on normal lymphatic circulation (44). The lymphatic system contains and fights any infection regionally between the site of entry and the lymph node (38). The lymph node removes pathogenic organisms by phagocytic activity and by exposure to lymphocytes within the node itself or by adding to the existing population of defensive cells circulating in the lymph and blood (33). Any immunological response to foreign antigen, therefore, requires functioning lymphatics to transport that antigen to the regional lymph node (36).

II-2. PHYSIOLOGY OF LYMPH CIRCULATION:

To better understand the complexity of lymphedema, the exchanges that take place between the blood capillaries and the tissues must be considered. Two main processes are involved in the exchange of substances between the blood and the tissues.

These are:

1. Filtration. This process involves the movement of solvents across a selectively permeable membrane by gravity or mechanical pressure (35). The movement of fluid

back and forth across the semi-permeable membrane of the capillary wall is determined by the balance between blood pressure in the capillary (which tends to force fluid outwards) and the osmotic pressure of the plasma proteins (which tend to draw it back). At the arterial end of the capillary, blood pressure is high (30-70 mm Hg), and therefore fluid moves outwards, into the tissues (37, 45). At the venous end of the capillary, the blood pressure is lower (10-16 mm Hg), and the osmotic pressure of the plasma proteins tends to draw fluid back into the capillary (37, 45). The tension of the tissues is a further element that limits entry of fluid into the tissues while enhancing its return into the venous capillary. The surplus of fluid filtered out, over that reabsorbed, provides the small volume of fluid that is then removed from the tissues by the lymphatic system (41).

2. Diffusion. Diffusion is the primary process for the exchange of molecules across the capillary membrane. This exchange means that molecules pass backwards or forwards across the membrane, from a region of higher concentration to that of a lower concentration, independent of whether fluid is moving back or forth. The diffusion is limited because the capillary membrane is only semipermeable. Large molecules, such as protein, approaching in size the diameter of the pores in the capillary wall, have more difficulty passing across the membrane than smaller ones, so that fewer of them escape. However, the small amounts of protein that do escape from the capillary, along with other macromolecules in the interstitial fluid, can easily enter and be removed by the highly permeable lymphatic capillary (37, 40, 41).

II-3. PATHOPHYSIOLOGY OF LYMPHEDEMA:

Lymphedema has been defined as "tissue swelling due to a failure of lymph drainage" (46), and may have several causes. Since a function of the lymphatic system is to drain away interstitial fluid containing mostly water and proteins, extensive lymphatic obstruction would disable this process, and result in lymphatic outflow resistance and a rise in lymphatic pressure (46). If lymphatic drainage is not effectively compensated by collateral drainage (46) then the consequence is a dilation of the lymphatic vessel. Initially, the lymphatic collecting vessel responds to the increased vessel diameter by increasing the rate of smooth muscle contractility (34). In theory, if contractility fails, then the excessive dilation of the lymphatic vessel leads to valve incompetence and dermal backflow (46,47). The result is a swelling with high protein content (25, 46). The high level of protein in the tissues then disturbs the normal balance of hydrostatic and osmotic forces between the vessels and the extravascular spaces (Starling's forces), resulting in more fluid being moved into the tissues (48). Eventually, the progressive stretching of the skin and subcutaneous tissues by the excess fluid results in a reduction of the normal resistance to swelling provided by the tissues (49). If interstitial edema persists, then changes are thought to occur in the mechanical properties and/ or composition of the ECM, which lead to the eventual development of fibrosis and lipidosis (34). When fibrosis occurs, increased skin thickness, and a 'honeycomb' pattern of the soft tissue in the subcutaneous compartment are visible on Computed Tomography (50). This more solid form of edema may further inhibit lymphatic drainage and be more difficult to treat (50). As well, venous abnormalities in the lymphedematous limb have been found to coexist in up to 70% of patients, though, at present, their contribution to the swelling is still uncertain (50).

Lymphedema also favours development of local and/or systemic infection due to an impaired immune response in the region, and because the idle lymph fluid provides an ideal medium for bacterial growth (22, 38). Added to this, any local inflammation resulting from injury or infection will cause increased capillary permeability, and thereby accelerate the loss of protein and fluid from the vascular system into the interstitial spaces and worsen the swelling (48).

II-4. ETIOLOGY OF BREAST CANCER RELATED LYMPHEDEMA:

The incidence of lymphedema is primarily related to the extent of the axillary dissection at surgery and to the exposure of the axilla to radiotherapy (51). Other precipitating factors that have been implicated in the development of lymphedema are: infection in the ipsilateral limb, obesity, hypertension, air flight travel, and presence of cancer in the lymph nodes (52). Lymphedema development appears to be unrelated to drug therapy administration or surgery to the breast (52). Inconsistencies exist in the literature with regards to risks associated with patient age, arm dominance, and radiation to the breast (53).

Surgical procedures used in the treatment of breast cancer normally involve the removal of lymph nodes, and thus surrounding portions of attached lymphatic vessels are also resected (38). It is not known whether lymphatic regeneration can bridge the "gap" of the surgical excision especially when complicated by infection or excessive scar tissue. In the post-surgical period, when the limb is free of lymphedema, dilation of the main collecting lymphatics can be visualized by lymphangiography (38).

Lymphatic vessels are relatively insensitive to radiation, maintaining their structure and function (53). However, radiation does impede the normal regeneration of lymphatic vessels after surgery, and the lymphatic vessel constriction seen late post-radiotherapy is thought to be due to the development of surrounding soft tissue fibrosis (53). Lymph nodes, on the other hand, are sensitive to radiotherapy, responding first with lymphocyte depletion, followed by fatty replacement and then by fibrosis (53). Functionally, radiation appears to impair the filter function of the radiated lymph nodes and to weaken their immune function (53).

II-5. OVERVIEW OF TREATMENT FOR LYMPHEDEMA:

At present there is no standard approach for treating lymphedema (54). Megens et al. (1998) examined 13 investigations and found most studies used a quasi-experimental design with a one-group pre-test/post-test format (55). Recommendations for future research included incorporating blind assessment of outcomes, random assignment of subjects to groups, and consensus on an outcome measure that yields valid and reliable data for the evaluation of limb size while allowing for comparison of results across studies (55). Recently, the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer highlighted the need for randomized controlled trials to determine effective therapies for lymphedema (56).

Since lymphedema is a chronic condition, the various conservative treatments aim to reduce and maintain limb size to restore function, to reduce pain, and for cosmesis. Physiologically, treatments are based on increasing lymph flow from the limb, minimizing the formation of new lymph, and/or encouraging resorption of fluid into the venous capillaries. Such treatments normally include education, elevation, exercise, compression therapies, MLD and CPT.

II-5-a. Education

From an educational point of view, it has been recommended that patients be instructed in proper arm and skin care to avoid injury to, and infection in, the limb (25). As lymphedema is a chronic condition, a basic understanding of the condition and its treatment, with an emphasis on realistic outcomes of treatment (management rather than cure) has been suggested (19).

II-5-b. Elevation

Elevation is the most common suggestion given to patients with lymphedema (32). Elevation of the limb decreases the intravascular hydrostatic pressure and as a result, fluid movement into the tissues should be reduced (32). Elevation alone, however, has not been shown to be an effective treatment for lymphedema (57).

II-5-c. Exercise

Although there have been no scientific studies on the effect of exercise or different exercise protocols on lymphedema, it is known that skeletal muscle contraction is a primary force propelling lymph fluid through the lymphatic system (48). Changes in intrathoracic pressure that occur during the respiratory cycle and specifically with abdominal breathing, also increase lymphatic flow (58). Aerobic-type exercise, therefore, could potentially facilitate this process but has not been investigated. An isometric upper extremity exercise program, carried out while wearing bandages or a compression sleeve, has been designed but has not been validated (59). In the clinical setting, however, women often report an increase in swelling with use of the arm for functional activities and with exercise (58).

II-5-d. Compression Therapies (CT)

Compression sleeves (garments) are available in prefabricated or custom-made styles and are generally used to maintain limb volume following reduction treatment. Compression sleeves exert a gradient pressure on the tissues of the limb, with more pressure exerted distally (47). Theoretically, the sleeves increase tissue pressure thereby reducing fluid leakage out of the capillaries and increasing fluid return into the venous system (32). The sleeves have a high elasticity component and as a result, the sleeves have a higher resting pressure and exert a lower pressure when the arm muscles are contracting (47). Attaining patient compliance in wearing a compression sleeve can be difficult, as the sleeves may be uncomfortable initially and are often more visible than the actual swelling (13). Bertelli et al. (1992), in a randomized controlled study found no significant difference between two treatment groups (electrical stimulation and intermittent pneumatic compression) when compared to the control group using a compression sleeve alone (60). The compression sleeve resulted in a 14.7% reduction in lymphedema.

Intermittent pneumatic compression (compression pump) has traditionally been considered an effective form of treatment for lymphedema (61, 62). However, studies have indicated that ongoing treatment with the compression pump (1.5 hours per day) is necessary to maintain any volume reduction in the limb (63). Compression pumps are not recommended for patients with lymphedema involving the chest wall (64), as potentially, the pump will move more fluid proximally into an already congested region. More recently, Dini et al. (1998), in a randomized study (n = 80), found no statistically significant difference between the reductions in lymphedema volume achieved by subjects receiving compression pump treatments when compared to subjects in the control group receiving no treatment (65).

Multi-layered compression bandaging (CB) is a technique used to maintain limb volume between treatments and as a form of compression to the limb. CB is applied with low stretch tensor bandages, and as such, CB applies lower pressure than standard elastic tensor bandages. CB works on the principle of increasing tissue pressure and is believed to enhance the muscle pump effect on the lymphatics by providing a resistance to contracting muscles (66). In contrast to compression sleeves, the application of low stretch bandages results in a low resting pressure and a high working pressure (47) on the tissues. Bandages are reapplied daily and can accommodate a rapid change in limb volume. If compression is not applied to the limb, the laxity of the tissues, stretched by the swelling, allows almost instant refilling of fluid into the tissues (25). In one prospective study of patients with severe lymphedema (n = 13), a 36% median reduction was achieved after 4 days of bandaging, self-massage and exercise (30). More recently, Badger et al., (2000), randomized 78 subjects to either eighteen days of CB (n = 32) followed by a maintenance program using compression garment, or to use of a compression garment alone (n = 46) (47). They found a significantly larger difference (p= 0.001) in the reduction in limb volume at twenty-four weeks in the group receiving CB (31%) when compared to the group wearing a compression garment alone (15.8%). However, the sample in the Badger study was not limited to breast cancer related lymphedema and included subjects with lower extremity lymphedema. As well, the lymphedema volume was measured by either circumference measurements or by an electric volumeter and data were combined. Details were not provided on the agreement between the measurement methods or on the reliability of the assessor performing the measurements.

II-5-e. Manual Lymph Drainage (MLD)

MLD is a specialized, gentle massage technique that stimulates lymphatic flow. The technique attempts to access collateral lymphatics to draw fluid from impaired regions to areas of normal lymphatic functioning. In support of this theory, MLD applied to the contralateral quadrant has been shown to increase the lymphatic transport rate of an injected tracer from a lymphedematous limb (25). To maintain any reduction achieved by the MLD, compression must be applied to the limb between treatment sessions to prevent refilling of the fluid into the tissues. Thus, MLD is not believed to be an effective intervention when used in isolation (25). Zanolla, et al. (1984), evaluated the effectiveness of two different pump regimes and MLD, and found a significant reduction in lymphedema in post-mastectomy patients receiving MLD in conjunction with a compression garment (61). The authors reported that the sample size (n = 60) was too small to compare the different treatment groups being studied. Hutzschenreuter (1991), in a retrospective quasi-experimental study, showed that MLD combined with CB decreased arm lymphedema volume by 20% (67). Johansson, in a randomized controlled study (n = 28), compared MLD to Intermittent Pneumatic Compression and found that MLD in combination with a compression sleeve reduced arm volume by 15% (68). Although there was a larger reduction in the group receiving MLD, no statistically significant difference was found between the groups. In a later investigation (1999), Johannson, in a prospective, nonrandomized study, compared MLD in combination with CB to CB alone (n = 38) (31). The treatment period was three weeks in total, with two weeks of CB followed by one week of combined MLD and CB, or CB alone. A statistically significant difference (p= 0.04) was found in the additional percentage volume reducing effect of MLD (11%) to that of CB (4%); however, no significant difference was found between groups in absolute volume reduction (47 mL vs. 20 mL). Though questionable whether these small differences would be clinically significant, the decrease in limb tension and heaviness reported in the MLD group (p= 0.03) is of interest. As well, it was not known whether the effect of the MLD would have been greater if it had been applied, as is normally done clinically, for more than a one-week treatment period.

II-5-f. Complex Physical Therapy (CPT)

CPT is a combination of treatment techniques. It consists of daily MLD and CB, meticulous skin care and a specialized exercise program. The treatment program is normally 4 weeks long followed by a maintenance period. Foldi, (1989) in a retrospective study, reported on 399 patients with lymphedema and no active cancer who had received CPT, and found a reduction of more than 50% in 56% of cases, between 25% and 49% in 31% of cases, between 1% and 24% in 8% of cases, and no reduction or an increase in 5% of cases (25). Morgan's one group pretest/ post test study of 78 post-mastectomy patients found that after a four-week course of CPT, volume was reduced by a mean of 50% (28). Ko et al., (1998) in a similar study, reported a mean edema reduction of 59% (28), while Boris et al., (1997) reporting on 56 consecutive arm lymphedema patients treated with CPT, found average reductions of 62.6% (69). Analysis at follow-up in the Boris study, 36 months later, showed an increased reduction to 79% in patients compliant with the maintenance program and a regression to 43% in noncompliant patients. The results of 113 patients with breast cancer related lymphedema, receiving a four-week course of treatment similar to CPT, in the Rehabilitation Department of the Cross Cancer Institute, showed a mean edema volume reduction of 52% (70). Matthews et al. (1996), in a prospective nonrandomized trial examined a modified version of CPT, with MLD treatments provided only twice per week, and no significant difference was found between the lymphedema reduction in the modified program (n= 20) when compared to the full program (n= 5) (71). Though the results seem to favor a modified program, the study was limited by unequal group sizes and a small sample (n= 25). As well, in the study, normal fluctuations in limb size were not controlled for, as measurements were not consistently taken of both the affected and unaffected arm. More recently, Andersen et al., (2000) randomized forty-four patients to receive CPT with or without MLD (72). The CPT protocol replaced the CB component with compression garments. The compression garment protocol involved the use of progressively smaller garments as the arm volume decreased. Thirty-eight subjects completed the trial. No statistically significant difference was found with the addition of MLD. The reported mean reduction was 60% with the progressive compression sleeve regime, exercise and education. The validity and reliability of the measurement procedures used in the Andersen study were not reported and independent assessors were not used. Positive results from CPT have been shown using fluorescence microlymphography, pressure measurements in cutaneous lymph capillaries (73) and by comparing lymphscintigraphy results before and after CPT (74). Unfortunately, the actual effect of the individual components of CPT, shown on these tests is not known, and results were not found to consistently correlate with clinical outcomes.

II-6. SUMMARY:

The physical therapy intervention options for lymphedema vary from simple to highly specialized treatments. The treatment time involved and the costs of treatment vary considerably and may be expensive and inhibitory. The uncertainty as to which techniques or combination of techniques are most effective makes choices difficult for both patients and practitioners. The research investigations performed to date have been limited by their design and/or small sample sizes and have provided little guidance in these matters. The focus of the present study was on MLD and CB. These two components were chosen as they both required special expertise and training on the part of the physical therapist, yet a vast difference exists in the cost of their application. This cost difference is primarily in the overall one-on-one patient/therapist treatment time, with MLD costing four to fives times as much as CB. Exercise was not examined in this study due to the numerous variables associated with exercise prescription. The purpose of the present study was to compare the reduction in lymphedema volume from MLD in combination with CB to CB alone by use of an experimental design and blinded assessment of outcome measurements. The rate of lymphedema reduction was also analyzed, to provide insight into the effect of the treatments over time. Two reliable methods of assessing lymphedema volume were used in order to establish concurrent validity and to allow for comparison of results to other studies.

III: CHAPTER THREE

METHODS AND PROCEDURES

III-1. SUBJECTS:

A convenience sample of breast cancer patients was used. Potential subjects were identified by referral to the Rehabilitation Department at the Cross Cancer Institute (CCI). The CCI provides assessment and treatment for all cancer patients in Northern Alberta. The Rehabilitation Department of the CCI offers a specialized program for the treatment of all cancer-related lymphedema and sees, on average, 95 new cases of breast cancer related lymphedema a year. The advantage to using the CCI was that, based on estimated breast cancer and lymphedema incidence rates, the majority of lymphedema patients in Northern Alberta are likely seen in the CCI Rehabilitation Department and thus an adequate sample base was anticipated.

III-2. SAMPLING SIZE:

Sample size was calculated for a prospective study using sample size calculations for treatment studies (75) based on an alpha of 0.05 and a power of 80%. The alpha of 0.05 and the corresponding power of 80% were chosen as they represent reasonable protection against Type I and Type II errors respectively (76). The expected standard deviation was determined by using clinical results from the Cross Cancer Institute, Lymphedema Program. The required sample size for the study was 42 subjects or 21 subjects per group to detect a difference of 20% in the reduction of lymphedema between the two groups. The effect size was determined from clinical results and from the review of the literature. (The postulated result for the combined MLD and CB group was a mean reduction of 50% while the CB group was anticipated to achieve a mean reduction of 30%.) Appendix G contains the sample size calculations. Based on the time commitment of four weeks of treatment and the requirement of constant bandaging, an attrition rate of 20% was anticipated. Therefore, 4 subjects per group were added, giving a starting sample size of 50 subjects.

III-3. INCLUSION CRITERIA:

The subjects who participated in this study were females with diagnosed breast cancer. Subjects had undergone unilateral breast surgery including an axillary node dissection. For the purposes of the study, subjects were required to have a medical diagnosis of lymphedema as determined by the primary care physician, surgeon and/or oncologist. Clinically significant lymphedema was defined as a minimum of a 150 mL difference between the affected and unaffected arms. This definition was chosen, as it is known that in 95% of normal subjects, the normal asymmetry of the limbs does not exceed 150 mL (77). None of the subjects had received active treatment for lymphedema within the six-month period prior to entering the study. Subjects were not excluded if they were using a compression sleeve for maintenance. However, to control for any potential treatment effect from the sleeve, any compression sleeve worn was required to be at least four months old. Consent to participate was obtained from the referring physician and subjects provided signed Informed Consent.

III-4. EXCLUSION CRITERIA:

To control for other variables that may have affected the results of the study, subjects were excluded from the study if:

- They had evidence of distant cancer metastases or local cancer recurrence
- Radiotherapy or chemotherapy was being administered to the subject
- There were signs of infection in the affected limb (redness, rash, red streaks, heat, pain)
- There was evidence of contraindications to treatment: uncontrolled hypertension, heart disease, renal insufficiency, venous thrombosis

A screening chart (Appendix H) was used to record all inclusion and exclusion criteria. The exclusion criteria were screened for by subject interview, chart review, on initial physical therapy assessment and, if necessary, information was verified by contact with the subject's physician. Subjects were to be removed from the study if they presented, at any time during the study, with any exclusion criteria.

III-5. STUDY DESIGN:

The study was a randomized, controlled-treatment study to determine if there was any significant benefit to the addition of MLD in the reduction of arm lymphedema volume in women receiving CB treatment for breast cancer related lymphedema. This experimental design (Figure III-5-1) was chosen to control for confounding variables and systematic bias that may occur with other designs such as self-selected groups or a one group pre-test/ post-test format. Some bias was controlled for by use of random assignment of subjects to groups, and other effects, such as maturation and history bias, were expected to be equal in both the treatment groups. Subjects were randomized to one of the two treatment groups by use of a computer-generated code developed by the statistician at the Cross Cancer Institute. The allocation sequence was concealed from research personnel involved in screening, scheduling and enrolling participants.

Group 1: Combined manual lymph drainage and multi-layered compression bandaging (MLD/CB)

- Manual lymph drainage x 45 minutes
- Multi-layered compression arm bandaging

Group 2: Control group (CB)

- Multi-layered compression arm bandaging

All subjects received four weeks of treatment. Standard education on proper arm and skin care was provided (Appendix I). Subjects in Group 1 received daily MLD. The MLD treatments were provided primarily by one physical therapist (Principal Investigator) trained in the Vodder Method of MLD, Monday through Friday. Two other Vodder trained therapists, assisted, as needed, with the provision of treatment. The same practitioner (Rehabilitation Assistant) bandaged subjects in Groups 1 and 2, Monday to Friday of each week. All research personnel were employed at the Cross Cancer Institute. The bandages were worn between treatments and were to be removed only if discomfort occurred. Subjects were provided with a temporary compression garment to wear in the event that the bandages had to be removed. Measurements were taken on admission to the study and at the end of week 1, week 2, week 3, and week 4. All treatments and measurements were done at the Cross Cancer Institute.

Group 1 (MLD/CB) xi------x1--------x2------x3------x4

↗

Subjects --------randomized

↘

Group 2 (CB) xi------x1--------x2------x3------x4

day 1---------------------------day 28

xi= initial testing
x1= testing end of week 1
x2= testing end of week 2
x3= testing end of week 3
x4= testing end of week 4

Figure III-1. : Study Design

III-6. DATA COLLECTION:

III-6-a. Variables

The dependent variable in this study was the volume of lymphedema in the affected arm. The lymphedema volume was determined by comparing the difference in arm volume between the affected and unaffected arms. Thus each subject's unaffected arm served as a control. The difference in lymphedema volume from initial measurement to the final measurement, at the end of week four, represented the change score. The primary endpoint, therefore, was the change in lymphedema volume over the four-week treatment period as determined by water displacement volumetry. The changes in lymphedema volume were expressed in both milliliters and percentage reduction. The percentage reduction (percentage of the excess volume reduced by treatment) was calculated as follows:

$$\frac{\text{difference initial} - \text{difference week 4}}{\text{difference initial}} \times 100$$

where difference = affected arm volume minus unaffected arm volume

The independent variables in this study were manual lymph drainage (MLD) and time. Manual lymph drainage is a gentle specialized massage technique that stimulates lymph flow by applying gentle pressure and stretch to the tissues. In this technique, the neck and contralateral upper quadrant were massaged first, to stimulate lymph flow. The massage sequence commenced proximally, with massage strokes applied in a distal to proximal direction (in the direction of normal lymph flow). The limb was massaged in segments starting proximally at the shoulder and moving progressively down the arm. The massage sequence avoided the damaged lymphatics in the axillary region, and attempted to access alternative lymphatic vessels from the outer aspect of the arm to drain the fluid from the limb (Appendix A).

The second independent variable in the study was time. Measurements were taken on a weekly basis to examine the effect of treatment over time and to determine if there was a difference in the rate of lymphedema reduction between the two groups.

Both groups received multi-layered compression bandaging. Short stretch bandages were used and were applied in a supportive rather than compressive manner. The pressure applied by the CB was greatest at the distal end of the limb and was achieved by applying more layers distally, and gradually reducing the number, and overlap, of the bandages as applied proximally along the arm. At the start, a cotton tube stockinette was placed on the arm. A primary layer of gauze was applied to the fingers and hand. A layer of 1/2 centimetre foam padding was placed on the hand and wrapped around the arm. Three or four bandages (4 cm, 6 cm, 8 cm and 10 cm) were placed around the limb with the first bandage starting at the hand, the second bandage starting at the wrist and the third bandage starting just below the elbow (a fourth bandage was necessary for larger arms). All bandages were applied in a figure of eight fashion (Further information on procedures and bandaging materials are provided in Appendix B). Bandages were left in place continuously and were not removed until the next scheduled treatment. In a small pilot study on four subjects, the average pressures in millimeters of mercury applied to the hand, forearm, elbow and upper arm were: 22, 17, 14 and 10 respectively (Appendix B).

Intervening variables that may account for variations in arm volume are fluid retention that may be diet or menstruation related, weight gain or loss, and normal diurnal fluctuations. The normal daily fluctuation in limb volume is reported to range from zero to 66 mL (78). To control for these variables, the volume of both arms was measured and compared at each assessment, body weight recorded, and measurements were made at approximately the same time of day, each time. Subjects were also asked to provide information on any medications and vitamins used during the study period. To date, there is no evidence of interaction between specific medications or vitamins and arm lymphedema volume; therefore, this information was collected for future reference only.

III-6-b. Demographic Information

Type and stage of breast cancer, type of surgery, number of nodes removed on axillary nodal dissection, occurrence of post-operative infection, age, radiotherapy administration, chemotherapy administration, time since surgery, duration of lymphedema, initial lymphedema volume, and arm dominance were noted. The stage of cancer was based on the pathological stage, which followed the TNM (tumor, nodes, and metastases) classification system (51). Chemotherapy treatment was divided into three classifications: standard (combinations including any of adriamycin, cyclophosphamide, methotrexate, 5 fluoracil), moderate (combinations including taxotere/taxol) and high dose (more than one combination of chemotherapeutic regimes and/or stem cell transplant). Initial demographic and medical information were obtained from the medical referral form, medical chart and by the interview process.

III-6-c. Monitoring of Weight as a Potential Confounding Variable

Body weight was recorded for the purposes of monitoring a potential intervening variable affecting arm volume. Body weight was assessed using a calibrated balance beam scale to the nearest 0.1 kg. Subjects were weighed at each measurement session. The scale was calibrated before the measurement of each subject. Subjects were weighed in a hospital gown with shoes off (Appendix K).

III-6-d. Measurement

Two measurement methods were used for assessing lymphedema volume. It was felt to be of clinical interest to determine if the volume calculated from circumference measurements provided a valid estimate of arm lymphedema volume as determined by water displacement volumetry, and if, the findings would be similar across both water displacement volumetry and the volume calculated from circumference measurements. The collection of data from the two methods would also allow for comparison of results to other studies utilizing either of these outcome measurements.

III-6-d-i. Water Displacement Volumetry

The primary outcome measurement was lymphedema volume as determined by water displacement volumetry. Volumetry is a measurement technique based on the principle of water displacement. The limb is immersed in a water tank to a controlled depth. The overflow is collected and measured (79). This method is considered the "gold standard" as measurements have consistently proven to be reproducible with an error of less than one percent (78, 79, 80). The error of method has been found to be 10 cc (78). Kissen et al., (1986) in comparing subjective lymphedema (patient plus observer impressions) to objective (physical measurement) assessment, found that arm volume as determined by volumetry (measured to 15 cm above the lateral epicondyle), was a more sensitive measure of lymphedema than a proximal arm circumference measurement (5). The main disadvantage to using water volumetry is that, due to the position of the outflow spout, the upper 3 to 4 centimetres of the arm are not included in the measurement. Water volumetry procedures were followed (Appendix J) and arm volume was recorded on a data collection sheet (Appendix K).

III-6-d-ii. Measurement of Circumference

The secondary outcome of interest was lymphedema volume as calculated from limb circumference measurements. Circumference (girth) measurements are simple, efficient and used more commonly in the clinical setting. Circumference measurements also provide information on the measurements at the upper-most aspect of the arm, the location of the lymphedema, and on where changes in girth occur during treatment. There are many different suggested measurement locations and procedures in measuring circumference of the arm (10). For the present study, circumference measurements were taken of both arms, starting at the finger MCP joints, across the hand including the thumb MCP and wrist. As well, circumference measurements at 4-cm intervals from the wrist to axilla were taken. Arm volume was then calculated based on the formula for a truncated cone (Appendix L). Using the same measurement technique and formula, Karges et al., (1996) reported the correlation between the calculated volume from circumference measurements and the total water displacement volume as $r = 0.99$ and the coefficient of determination (r^2) as 0.98 (80). The reliability of the circumference measurements, expressed as an intra-class correlation coefficient (ICC), ranged from 0.96 to 0.99 and the standard error of measurement was reported as 0.09 cm to 0.20 cm (80). For the present study, a non-stretch fiberglass tape measure, with intervals of 0.1 cm, was used to measure both the circumference and the length of the upper extremity. Detailed measurement procedures were followed (Appendix M) and a Circumference Measurement chart (Appendix N) was used to record the data.

III-7-e. Exploratory Analysis: Percent reduction by degree of Lymphedema Severity

For the purposes of exploratory subgroup analysis, subjects were divided into three groups (mild, moderate and severe; see Definitions Section I-4.) based on the percent volume increase in the affected arm (Definition Section I-4), on commencement of the study. The classification of lymphedema by degree of lymphedema severity remains subjective. The subgroups were determined from clinical experience and represent a modified version of previously developed classifications (49, 79). Clinically, the presentation of an absolute lymphedema volume of 300 mL or less represents a mild lymphedema, and a volume greater than 750 mL a severe lymphedema. A volume of 2000 mL was chosen as the standard for the unaffected arm (77) and, based on the absolute lymphedema volumes, the relative percentage volume increase for mild and severe lymphedema were determined as follows:

$$\frac{300\text{ mL}}{2000\text{ mL}} = 15\% \ (< 16\% = \text{mild}) \qquad \frac{750\text{ mL}}{2000\text{ mL}} = 37.5\% \ (> 37.5\,\% = \text{severe})$$

Moderate lymphedema represented the percentage volume increase from 16% to 37.5%.

III-6-f. Procedures

A designated physical therapist was responsible for screening lymphedema referrals to the Rehabilitation Department. Verbal confirmation of a patient's interest in the study was obtained over the phone by clerical staff (Appendix O) and interested individuals were sent an information letter. When inadequate information was available to allow for screening, an appointment was booked for a standard physical therapy assessment. The designated physical therapist completed the screening following the initial assessment. If the individual was interested in participating, an information letter was provided. The principal investigator (PI) phoned within one week asking whether the patient would be willing to allow the initial interview to occur. (Clerical staff was then responsible for booking the interview date and time.) During the initial interview, the PI reviewed information in the letter, explained the rationale behind the study and answered any questions from the patient. Once the subject agreed to participate in the study, and provided the subject met the inclusion/ exclusion criteria, informed consent was obtained. The subject was then randomized to one of the two treatment groups. Initial demographic and medical information was obtained from the medical referral form and by the interview process. Information on basic demographics was recorded on a data collection sheet (Appendix P).

Two independent assessors (IA) administered the outcome measurements. The independent assessors were qualified physical therapists familiar with, and trained in, the measurement procedure. The same IA was responsible for all measurements of a single subject. IA-1 measured subjects 1 through 42. IA-2 measured subjects 43 to 50. To control for potential observation bias, the independent assessors were blinded to the treatment groups and subjects were told not to discuss their treatment with the independent assessor. Entry of demographic data was the responsibility of the PI. The IA's entered the results obtained from their own independent measurements.

The accuracy of the volumeter was established prior to study initiation (Appendix Q). This was achieved by comparing the volume of water added to the volumeter to the volume of water displaced. Predetermined amounts of water were measured, added directly into the volumeter and the overflow was measured. The displaced water volume accounted for 99.6% of the actual water volume added to the volumeter. The mean volume difference was -6 mL (+/- 4 mL) for an average volume of 1600 mL. A second test was performed using a surgical glove and plastic sleeve to replicate a hand and arm respectively. The glove/ sleeve were filled with water and lowered into the volumeter. The volume of the displaced water, from the replicated hand or arm, accounted for 98.7% of the volume added to the volumeter. The mean volume difference was -16 mL (+/- 12 mL) for an average volume of 1232 mL. Therefore, overall, the volumeter was found to be accurate within 1%.

Intra-rater reliability of the IA (IA-1) was also established prior to the studies initiation. In a pilot study using 6 subjects (12 limbs), the IA-1 measured both arms of all 6 subjects using both circumference measurements and volumetry. Each subject's arm was measured 3 times, within a one-hour period. The IA-1 was blinded to the previous measurements. A total of 36 measurements were taken of each method (3 measurements per arm). An intra-class correlation (ICC) was used to determine the consistency of the IA when measuring arm volume. An ICC of 0.90 within each method was considered acceptable (76). IA-2 replaced IA-1 for the last two months of the study. The intra-rater reliability of IA-2 was therefore established during the study period. The ICC for water volumetry ranged from 0.990 for IA-1 to 0.998 for IA-2. The ICC for the volume calculated from circumference measurements for both assessors was 1.00. Inter-rater reliability of the two assessors was also assessed. In a pilot study of 4 limbs, the assessors measured each arm by water volumetry and by circumference measurements. The ICC for water volume was 0.990. The ICC for circumference measurements was 0.985. Therefore the ICC's in the reliability study were above the acceptable level. Appendix Q contains the data for the pilot studies.

III-6-g. Assumptions

The demographics and classification of lymphedema of the patients who agreed to participate in this study was not expected to differ from those who did not agree to participate. The reasons for refusal to participate included time constraints, foreseen difficulties with the requirement for constant bandaging, and a lack of interest in the study. As general population characteristics are not known, the results of the study can only be generalized to a population with similar characteristics.

III-7. STATISTICAL ANALYSIS:

III-7-a. Subject Demographic Information

Descriptive statistics were used to describe the two treatment groups on basic demographics and inferential statistics were used to determine comparability of the groups. An alpha level of 0.05 was used for the basic demographics as it represents reasonable protection against committing a Type I error (76). Table III-1 presents the method of analysis used for comparing the groups on demographic variables. The subject's medication and vitamin use were recorded for future reference but were not analyzed.

Table III-1

Demographics

Variable	Data	Descriptive Statistic	Inferential Statistic
Age	Interval	Mean and Standard Deviation	t-test independent samples
Type of Surgery	Nominal	Frequency/ Percentage	X^2
Nodes Dissected	Interval	Mean and Standard Deviation	t-test independent samples
Post-operative Infection (yes/no)	Nominal	Frequency/ Percentage	X^2
Radiation Field (axilla/ not axilla/ no radiation)	Nominal	Frequency/ Percentage	X^2
Chemotherapy (standard, moderate, high dose)	Nominal	Frequency/ Percentage	X^2
Time from Surgery (months)	Interval	Median and quartiles	median tests (non-parametric)
Duration of lymphedema (months)	Interval	Median and quartiles	median tests (non-parametric)
Cancer Type	Nominal	Frequency/ Percentage	X^2
Cancer Stage	Nominal	Frequency/ Percentage	X^2
Affected arm (dominant/ nondominant)	Nominal	Frequency/ Percentage	X^2
Initial Volume of Lymphedema	Interval	Mean and Standard Deviation	t-test independent samples

III-7-b. Results of Treatment

Descriptive statistics were used to describe the results of the treatment within each group and inferential statistics were used to determine if differences occurred within and between the groups. An alpha level of 0.05 was used for analyzing results. Table III-2 presents the method of analysis used for comparing the results of treatment.

Table III-2

Results of Treatment

Variable	Data	Descriptive Statistic	Inferential Statistic
Volumetry	Interval	Mean and Standard Deviation	▪ paired t-test within groups ▪ t-test independent samples between groups ▪ 2-way anova repeated measurements (rate of reduction)
Circumference Measurement	Interval	Mean and Standard Deviation	▪ paired t-test within groups ▪ t-test independent samples between groups ▪ 2-way anova repeated measurements (rate of reduction)
Association of measurements	Interval	Mean and Standard Deviation	▪ Pearson r
Exploratory subgroup analyses	Interval	Mean and Standard Deviation	▪ Two-way Anova (*Newman-Keuls test Probabilities for Post Hoc Tests*)

III-7-c. Weight

Descriptive statistics were used to describe the two treatment groups on both initial and final weight. Inferential statistics were used to determine if significant differences occurred within and between the groups for initial and final weight. Table III-3 presents the method of analysis for body weight.

Table III-3

Weight

Variable	Data	Descriptive Statistic	Inferential Statistic
Weight	Interval	Mean and Standard Deviation	▪ paired t-test within groups ▪ t-test independent samples between groups

IV: CHAPTER FOUR

RESULTS

IV-1. FLOW OF PARTICIPANTS THROUGH THE TRIAL:

Subjects were recruited from November 2000 to November 2001. Figure IV-1 presents the flow diagram of participants through each stage of the study. A total of 74 subjects were screened for eligibility and 63 subjects were initially deemed eligible to participate in the study. Ten subjects elected not to take part in the study. The primary reasons for non-participation were cited as the time commitment and/or the requirement of constant bandaging. Three subjects who had a medical diagnosis of lymphedema were subsequently ineligible, as they did not fulfill the requirement of a minimum of 150 mL of fluid volume difference between the arms. Therefore, of eligible subjects, the agreement to participate was 83.3%. Fifty subjects were enrolled in the study with 25 subjects randomly assigned to each group.

A total of 45 subjects completed the study. One subject in the MLD/CB group withdrew after she developed a skin reaction to the bandaging. Four subjects in the CB group withdrew; one due to illness of a family member, two as a result of dissatisfaction with treatment response, and one due to discomfort from the constant CB. One subject in the MLD/CB group, though completing the study, was excluded from analysis for the water displacement volumetry as an error was found in the recording of the arm volume.

Though data are presented on only 44 subjects for the primary outcome measure, the final number was within the projected sample size.

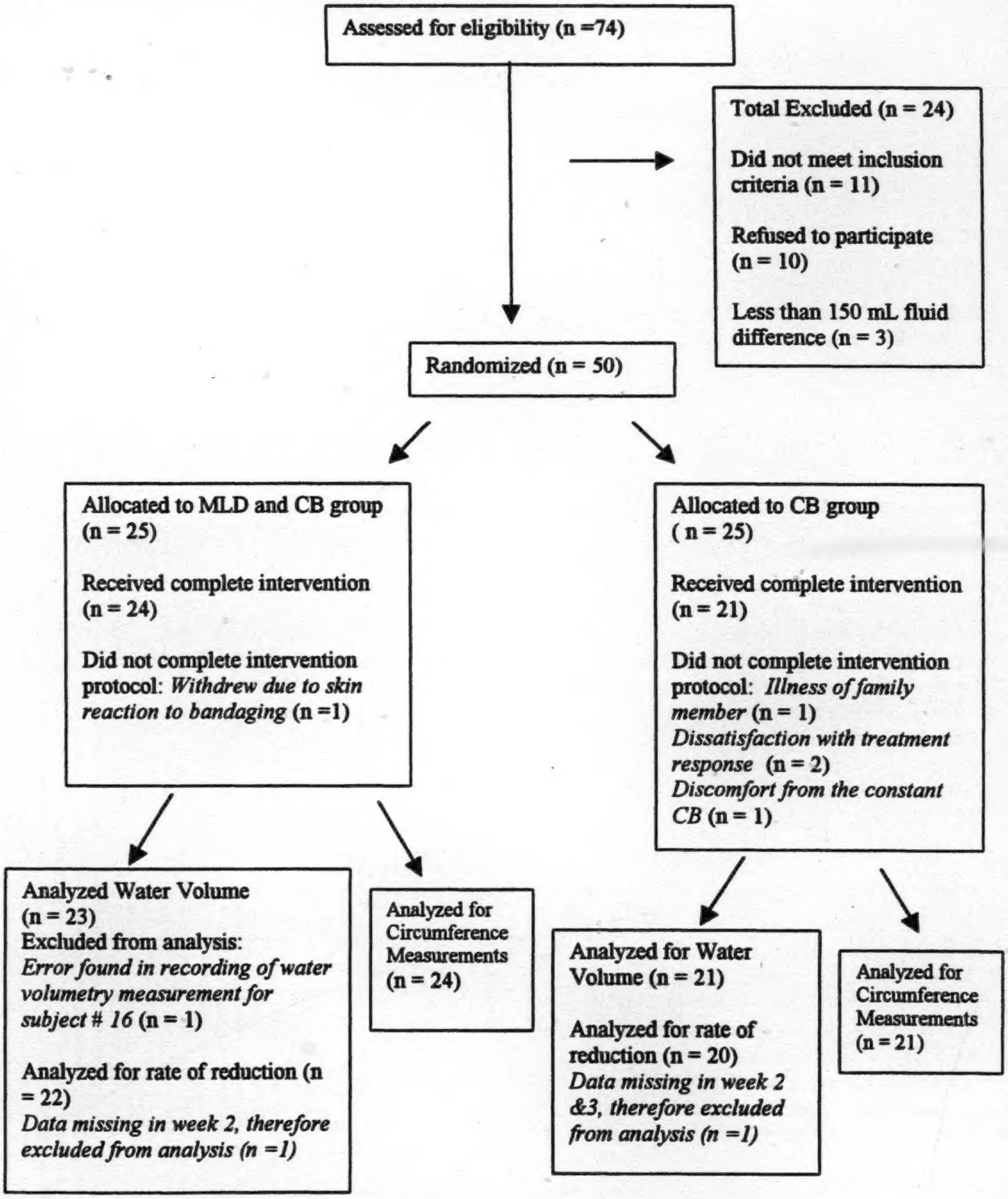
Assessed for eligibility (n =74)
Total Excluded (n = 24)
Did not meet inclusion criteria (n = 11)
Refused to participate (n = 10)
Less than 150 mL fluid difference (n = 3)
Randomized (n = 50)
Allocated to MLD and CB group (n = 25)
Received complete intervention (n = 24)
Did not complete intervention protocol: *Withdrew due to skin reaction to bandaging* (n =1)
Allocated to CB group (n = 25)
Received complete intervention (n = 21)
Did not complete intervention protocol: *Illness of family member* (n = 1)
Dissatisfaction with treatment response (n = 2)
Discomfort from the constant CB (n = 1)
Analyzed Water Volume (n = 23)
Excluded from analysis:
Error found in recording of water volumetry measurement for subject # 16 (n = 1)
Analyzed for rate of reduction (n = 22)
Data missing in week 2, therefore excluded from analysis (n =1)
Analyzed for Circumference Measurements (n = 24)
Analyzed for Water Volume (n = 21)
Analyzed for rate of reduction (n = 20)
Data missing in week 2 &3, therefore excluded from analysis (n =1)
Analyzed for Circumference Measurements (n = 21)

Figure IV-1. Flow diagram of participants through the trial

IV-2. SUBJECT CHARACTERISTICS:

Table IV-1 presents the demographic information for subjects completing the study (n=45). There were no significant differences (p > 0.05) between the groups on basic demographic information for randomized subjects (n =50) or when re-examined for subjects completing the study (n = 45). Of note was the large range in the initial volume of lymphedema, in the time from surgery and in the reported lymphedema duration (Table IV-1). This finding will be discussed further in Chapter 6. The data on the initial volume of lymphedema was not normally distributed therefore nonparametric tests were used to compare the groups.

IV-3. MONITORING OF BODY WEIGHT AS A POTENTIAL INTERVENING VARIABLE:

Table IV-2 presents the data on body weight in kilograms. No significant differences (p > 0.05) were found between groups or between the initial and final weight of the subject. Therefore, weight was controlled during the study period. The results of treatment were not influenced by weight gain or loss and represented a true change in lymphedema volume.

Table IV-1

Demographic Information

		MLD/CB n =24	CB n =21
Age (years)	Mean (+/- SD) and	58 (+/- 13)	63 (+/- 13)
	Range	33-78	40-87
Cancer Type	Ductal	19	14
	Lobular	5	5
	Mixed	0	2
Cancer Stage	Stage 1	7	8
	Stage 2	15	10
	Stage 3	2	3
Type of Surgery	Radical Mastectomy	0 (0%)	1 (5%)
	Modified Mastectomy	12 (50%)	11 (52%)
	Segmental Resection	12 (50%)	9 (43%)
Lymph Nodes	Number removed	12 (+/- 6)	10 (+/-5)
Radiation Treatment	Breast radiation only	6 (25%)	7 (33%)
	Axillary radiation	15 (63%)	11 (52%)
Chemotherapy Treatment	Standard	4 (17%)	4 (19%)
	Moderate	7 (29%)	1 (5%)
	High Dose	3 (13%)	1 (5%)
Post-operative Infection	(Yes)	n = 5 (21%)	n = 2 (10%)
Time from Surgery (months)	median/ range	39/ 2-281	45/ 3-386
	quartiles	20/ 62	14/141
Duration of Lymphedema	median/ range	21/ 2-219	19/ 1-194
	quartiles	6/ 34	4/103
Arm Dominance	dominant/ nondominant	11/ 13	10/ 11
Initial Volume of Lymphedema (mL)*	median/ range	535/ 165-3420	630/ 180-1395
	quartiles	245/ 720	382/ 892

* Data available for 23 subjects in MLD/CB group

Table IV-2

Subject Weight (Kg)

	MLD/CB **n= 24**	**CB** **n=21**
Initial Weight	79.2 (+/-18)	74.3 (+/-18)
Final Weight	78.9 (+/-18)	73.8 (+/-13)
Weight Change	-0.3 (+/-1.26)	-0.5 (+/- 1.33)

IV-4. RESULTS OF TREATMENT:

IV-4-a. Primary Outcome Measure: Water Displacement Volumetry

Table IV-4 presents the results of treatment as determined by water displacement volumetry. Initial and final volumes are presented; however, statistical analyses were performed on the more conservative delta change score. Significant differences in the reduction of lymphedema were found in both MLD/CB and CB groups from initial to final measurements. No significant difference was found between the groups in millilitre reduction (p = 0.812) or percent reduction (p = 0.297); therefore a reduction in lymphedema volume occurred over the time period irrespective of treatment assignment.

IV-4-b. Secondary Outcome: Circumference Measurement Results

The results from the circumference measurements were consistent with the results from water displacement volumetry. Table IV-5 presents the results as determined by the calculated volume from circumference measurements. Again, significant differences were found within each group; however, no significant difference was found between the groups in millilitre reduction (p = 0.88) or percent reduction (p = 0.368).

Table IV-3

Water Displacement Volumetry
Mean Difference from Initial Measurement to Final Measurement (Week 4)
Millilitre Reduction and Percentage Reduction (n =44)

	MLD/CB n= 23	CB n=21
Initial lymphedema volume	695 mL	672 mL
Final lymphedema volume	435 mL	426 mL
Millilitres Reduction (SD)	260 mL (+/- 217) *	246 mL (+/- 159)*
Percent Reduction (SD)**	46% (+/- 22)*	38% (+/- 16)*

* Statistically significant $p < 0.0001$ within groups (time effect)

** The percent reduction represents the mean of the relative reduction of each individual subject.

Table IV-4

Calculated Volume from Circumference Measurements
Mean Difference from Initial Measurement to Final Measurement (Week 4)
Millilitre Reduction and Percentage Reduction (n = 45)

	MLD/CB n= 24	CB n=21
Initial lymphedema volume	665 mL	656 mL
Final lymphedema volume	420 mL	402 mL
Millilitres Reduction (SD)	245 mL (+/- 227)*	254 mL (+/- 190)*
Percent Reduction (SD)**	44% (+/- 21)*	37% (+/- 18)*

* Statistically significant $p < 0.0001$ within each group (time effect)

** The percentage reduction represents the mean of the relative reduction of each individual subject.

IV-4-c. Exploratory analysis: Percent Reduction by Classification by Degree of Lymphedema Severity

To facilitate an understanding of the variation in treatment response, exploratory subgroup analyses were performed. Subjects were divided into one of three groups: mild, moderate or severe as determined by the percent larger of the affected arm when compared to the unaffected arm (definitions: Chapter I-5). Figure IV-2 shows the percent reduction by classification for the primary outcome measure water volumetry. Table IV-5 and IV-6 present the specific data for percent reduction by classification for water volumetry and circumference measurements respectively. A significantly larger reduction was found in the MLD/CB group for subjects with mild lymphedema when compared to subjects in all other subgroups.

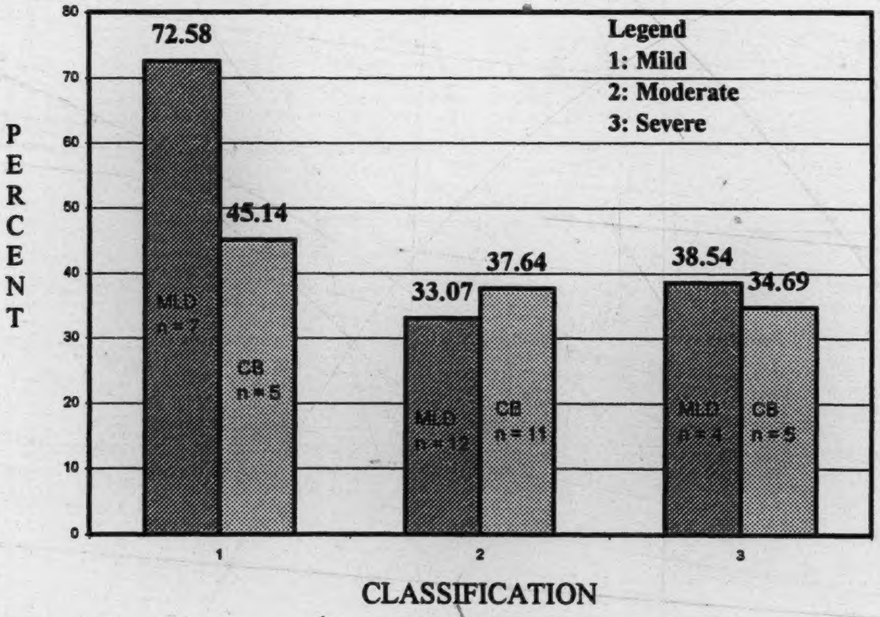

Figure IV-2

Percent Reduction by Classification
by Degree of Lymphedema Severity (n = 44)

Table IV-5

Results of Percent Reduction by Classification for Water Volumetry

General Manova	**Newman-Keuls test Probabilities for Post Hoc Tests**					
Group Percent reduction (SD)	**MLD/CB-mild** 72.67% (+/- 18)	**MLD/CB-moderate** 33.10% (+/- 11)	**MLD/CB - severe** 38.56% (+/- 13)	**CB-mild** 44.97% (+/- 20)	**CB-moderate** 37.66% (+/- 13)	**CB-severe** 34.71% (+/- 17)
MLD/CB mild		p < 0.001*	p < 0.001*	p < 0.003*	p = 0.001*	p < 0.001*
moderate	p < 0.001*		p = 0.919	p = 0.641	p = 0.856	p = 0.851
severe	p < 0.001*	p = 0.919		p = 0.459	p = 0.917	p = 0.895
CB mild	p < 0.003*	p = 0.641	p = 0.459		p = 0.673	p = 0.633
moderate	p < 0.001*	p = 0.856	p = 0.917	p = 0.673		p = 0.733
severe	p < 0.001*	p = 0.851	p = 0.895	p = 0.633	p = 0.733	

*Statistically significant

Table IV-6

Results of Percent Reduction by Classification for Circumference Measurements

General Manova	**Newman-Keuls test Probabilities for Post Hoc Tests**					
Group Percent reduction (SD)	**MLD/CB-mild** 72.19% (+/- 17)	**MLD/CB-moderate** 30.92% (+/- 8)	**MLD/CB - severe** 36.24% (+/- 9)	**CB-mild** 31.93% (+/- 25)	**CB-moderate** 42.75% (+/- 13)	**CB-severe** 33.22% (+/- 19)
MLD/CB mild		p < 0.001*	p = 0.024*	p < 0.004*	p < 0.017*	p < 0.003*
moderate	p < 0.001*		p = 0.995	p = 0.999	p = 0.623	p = 0.999
severe	p = 0.024*	p = 0.995		p = 0.999	p = 0.989	p = 0.999
CB mild	p < 0.004*	p = 0.999	p = 0.999		p = 0.880	p = 0.999
moderate	p < 0.017*	p = 0.623	p = 0.989	p = 0.880		p = 0.907
severe	p < 0.003*	p = 0.999	p = 0.999	p = 0.999	p = 0.907	

*Statistically significant

IV-4-d. Rate of Reduction

Measurements were taken on a weekly basis to determine if there was a difference in rate of reduction between the groups. Figure IV-3 presents the bar graph of lymphedema volume at each measurement session by group. There were no significant differences in the rate of reduction between the groups ($p > 0.05$); however, there was a reduction in lymphedema over time. As the main effect was time, data are presented for the total group. Table IV-7 presents the data on the rate of reduction by water volumetry and Table IV-8 presents the rate of reduction calculated from circumference measurements. The results indicate that there was a significant reduction in lymphedema volume between initial measurement and week one, week one and week two and week three and week four for the total group. Though a reduction occurred between week two and week three, it was not significant for the total group. The findings were consistent across both water displacement volumetry and circumference measurements for the total group.

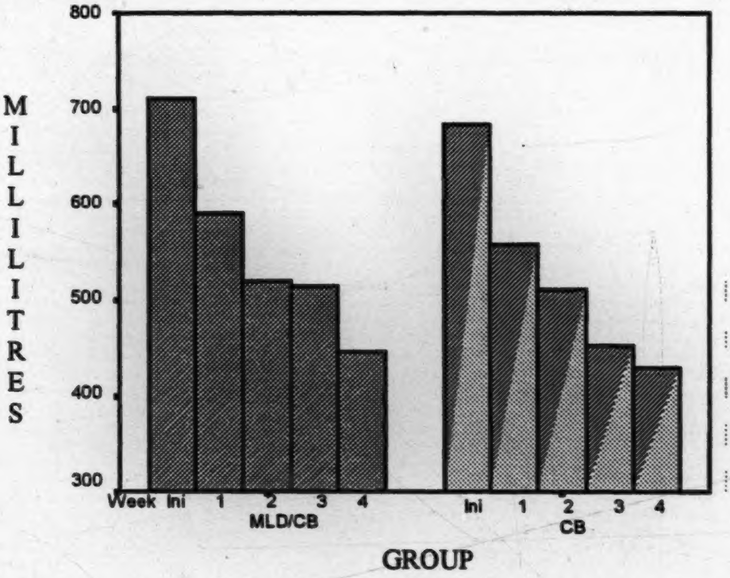

Figure IV-3

Remaining Lymphedema Volume by Week in Millilitres:
Average of the difference between the unaffected and affected arms (n = 45)

Table IV-7

The Reduction in Lymphedema Volume each Week as determined by Water Volumetry ($n = 42$**)

General Manova	**Newman-Keuls test Probabilities for Post Hoc Tests**				
Time	Initial Volume 700 mL (585)	Week 1 Volume 576 mL (514)	Week 2 Volume 517 mL (459)	Week 3 Volume 484 mL (441)	Week 4 (final) Volume 441 mL (435)
Initial		$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*
Week 1	$p < 0.001$*		$p = 0.003$*	$p < 0.001$*	$p < 0.001$*
Week 2	$p < 0.001$*	$p = 0.003$*		$p = 0.111$	$p < 0.001$*
Week 3	$p < 0.001$*	$p < 0.001$*	$p = 0.111$		$p = 0.032$*
Week 4	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	$p = 0.032$*	

* Statistically significant

** Two subjects (1 MLD/CB at week 2, 1 CB week 2,3) were missing data and therefore were excluded from the overall rate of reduction analyses

Table IV-8

The Reduction in Lymphedema Volume each Week as determined by Circumference Measurements ($n = 45$)

General Manova	**Newman-Keuls test Probabilities for Post Hoc Tests**				
Time	Initial Volume 664 mL	Week 1 Volume 539 mL	Week 2 Volume 478 mL	Week 3 Volume 453 mL	Week 4 (final) Volume 418 mL
Initial		$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*
Week 1	$p < 0.001$*		$p = 0.003$*	$p < 0.001$*	$p < 0.001$*
Week 2	$p < 0.001$*	$p = 0.003$*		$p = 0.111$	$p < 0.001$*
Week 3	$p < 0.001$*	$p < 0.001$*	$p = 0.111$		$p = 0.032$*
Week 4	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	$p = 0.032$*	

* Statistically significant

IV-4-e. Correlation between Water Volumetry and the Calculated Volume from Circumference Measurements

Figure IV-5 shows the scatter plot for the correlation between water displacement volumetry (Volumetry) and the calculated volume from circumference measurements for initial lymphedema volume and Figure IV-6 shows the scatter plot for final lymphedema volume. A significant correlation ($r > 0.80$) was found between the two methods in determining initial lymphedema volume (r = 0.985, p = 0.01) and final lymphedema volume (r = 0.987, p = 0.01).

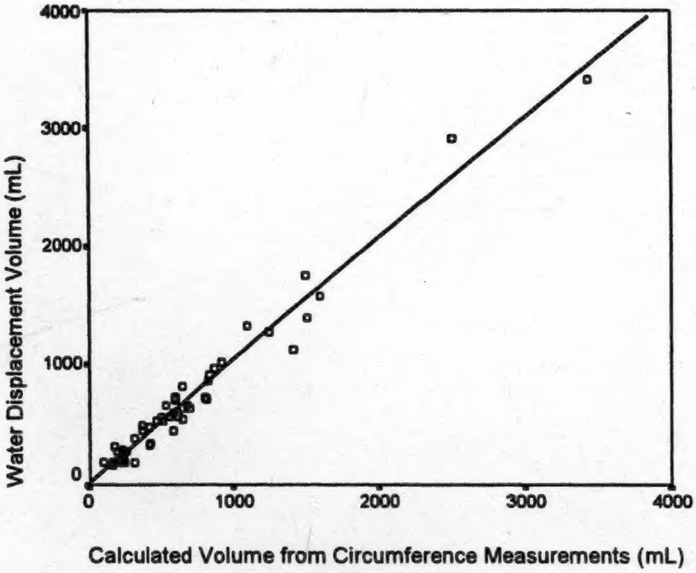

Figure IV-4

Correlation between Measurements in determining Initial Lymphedema Volume (n =49)

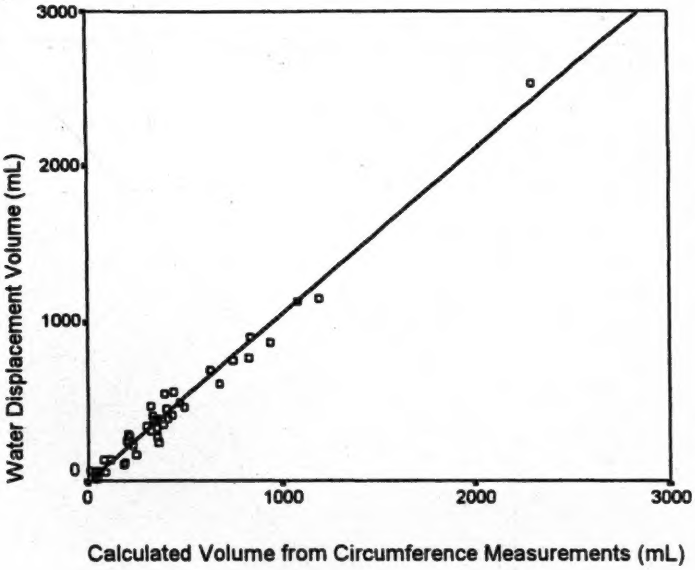

Figure IV-5

Correlation of Water Displacement Volume to the Calculated Volume from Circumference Measurements in determining Final Lymphedema Volume (n = 44)

IV-5. ADVERSE EVENTS DURING THE STUDY:

Two subjects complained of aching following the first application of bandaging; however, only one subject removed the bandages (in the late evening) due to the discomfort. For these two subjects, the bandaging application was modified to address the subject's own comfort issues and no further problems were encountered. One subject in the CB group withdrew in the second week of treatment due to discomfort in the elbow region from the constant CB. Another subject, in the MLD/CB group, was withdrawn in the second week of treatment as a result of a skin reaction (heat rash) to the bandaging.

V: CHAPTER FIVE

DISCUSSION

The purpose of this study was to examine the efficacy of MLD by comparing the reduction in arm lymphedema volume achieved from MLD in combination with CB to that achieved by CB alone. Two methods of determining lymphedema volume were used; the primary outcome measure was water displacement volumetry and the secondary outcome measure was the measurement of circumference. This section will be discussed in the following four subsections: 1) The effect of treatment within groups, 2) The effect of treatment between groups, 3) The rate of reduction, 4) The correlation between water volumetry and the volume calculated from circumference measurements.

V-1. THE EFFECT OF TREATMENT WITHIN GROUPS:

The first and second hypotheses (Chapter I-4) were supported by the findings of this study. A significant reduction in lymphedema volume was found within each group in both milliliter and percentage reduction, and the findings were consistent across both measurement methods (Table IV-3 and IV-4). These results indicate that MLD in combination with CB and CB alone are both effective interventions in reducing arm lymphedema volume.

V-2. THE EFFECT OF TREATMENT BETWEEN GROUPS:

V-2-a. Effect of Treatment: Initial to Final Measurements

The a priori third hypothesis that a significantly larger reduction in lymphedema volume would be found in the group receiving MLD/CB was not supported by the findings of the present study. Though a significant reduction in lymphedema occurred over time, the effect was independent of the treatment assignment. The lack of significance in lymphedema volume reduction between the groups is consistent with the findings of two other independent studies. Andersen et al., (2000) randomized forty-four patients to receive CPT with or without MLD (72). Though the CPT protocol replaced the CB component with compression garments, no statistically significant difference was found with the addition of MLD. Johannson et al., (1999) in a nonrandomized study compared MLD in combination with CB to CB alone (n = 38) and found no significant difference in absolute lymphedema volume reduction between the groups (31). In contrast to the findings of the present study, however, the authors reported a statistically significant difference ($p = 0.04$) in the additional percentage volume reducing effect of MLD (11%) to that of CB (4%).

CB has been found to be an effective treatment technique in previous reports (30,31,47). In the present study, the mean lymphedema reduction of 38% in the CB group exceeded the 25% to 30% reduction reported in the literature (31,47). The small differences in the reported relative reduction may, in part, be explained by differences in treatment protocol. In the Johannson study, the CB was replaced every second day (31) over a three-week period and the reported mean reduction was 26%. In the present study, the bandages were replaced daily (Monday through Friday) over a four-week period and the mean reduction was 38%. As the bandaging loosens with use of the arm, and over time, daily application of CB minimizes any potential for lymphatic fluid to reaccumulate in the arm, and may have accounted for the larger reduction from CB in this study. Another variation in treatment protocol was in the method of CB application. In conventional CB, bandages are applied in a spiral fashion on the limb (47,81). In the present study, the bandages were applied in a figure of eight fashion. Clinical experience has shown that the figure of eight is more effective in maintaining the bandaging position and is more comfortable.

Overall, it is evident that CB is an effective treatment technique. CB is also cost effective. The time required for the practitioner to apply CB is from ten to fifteen minutes and bandaging materials are relatively inexpensive. Practitioners in the hospital, clinic and homecare setting can be trained in the appropriate technique. Moreover, family members and/or even patients themselves, can, over time, be taught to effectively apply CB.

V-2-b. Exploratory Subgroup Analyses

A notable finding of the study was the large variation in treatment response among subjects, specifically with a clinical indication of interaction between severity of lymphedema and treatment response. In the present study, the affected arms of some subjects, particularly in the MLD/CB group, attained a "near normal state". As presented in Table IV-5 and IV-6, subjects with mild lymphedema in the MLD/CB group were found to have a significantly larger relative reduction with treatment than subjects in all other subgroups. Though this finding is the result of exploratory analyses, and may represent a false-positive finding, the information provides insight into potential future research directions.

Ramos et al., (1999) in a retrospective analysis of 69 women treated with CPT found that patients with 250 mL or less had a mean reduction of 78% while those with initial volumes of between 250 and 500 mL had a mean reduction of 56% (82). The authors concluded that the initial volume of lymphedema was critical in predicting the success of treatment. While the findings of the present study support the conclusion of Ramos et al., in theory, the response to treatment may also be dependent on the location of the lymphedema and the existence or absence of tissue fibrosis. In other words, the treatment response may reflect the extent of the damage to the lymphatic system. Though compromised, the lymphatic system in subjects with mild lymphedema would still be functioning to a larger degree than subjects with moderate or severe lymphedema. Functioning lymphatic vessels would be necessary for MLD to be effective in stimulating lymphatic flow and in establishing collateral drainage routes, and, may explain the significantly larger reduction seen in the mild group receiving MLD/CB. The effects of CB, on the other hand, are likely at the microvascular level. CB enhances tissue pressure, thereby limiting the filtration of fluid into the tissues and enhancing fluid return into the venous capillary. Perhaps for subjects with more extensive damage to the lymphatic system, compression remains the only effective means of reducing and controlling the edema.

V-3. THE RATE OF LYMPHEDEMA REDUCTION:

There were no significant differences in the rate of reduction between the groups; however, there was a reduction in lymphedema volume over time. The results of the study showed that the greatest reduction in lymphedema occurred in the first week, slowly diminished over the next two weeks of treatment (Tables IV-7 and IV-8) and slightly increased again in the final week. The results suggest that CB with or without MLD is most effective in the first 2 weeks. Leduc et al., (1998) found that the most important reduction in lymphedema occurred during the first week of a 10-day intensive treatment program that included MLD, CB, exercise and compression pump treatments (66). Johannson et al., (1999) reported significant reductions in lymphedema volume during the first two weeks of CB treatment (31). No significant reduction was obtained from CB treatment in the third week and thus, the authors concluded that CB is most effective when administered daily for two weeks. Clinically, for the majority of subjects in the present study, the volume reduction occurred rapidly in the first week of treatment and diminished over the rest of the treatment period. Some subjects, however, had a less dramatic and a slower response to treatment. Subjectively, on palpation at initial assessment, the affected limb of these subjects was described as "hard". This tissue firmness likely represented tissue fibrosis and may have negatively influenced both the rate and magnitude of the treatment response. Objectively, for these subjects, the best reduction was achieved in the final week of treatment and may account for the significant reduction achieved in the total group between week three and week four.

V-4. THE CORRELATION BETWEEN MEASUREMENT METHODS:

Two measurement methods were used for assessing lymphedema volume and to allow for future comparison of results to other studies. While previous studies have examined the relationship between the two measurement methods in determining arm volume, this is the first study to examine the concurrent validity between the two methods in determining lymphedema volume in women with breast cancer. The results of the present study showed a high correlation between the two measurement techniques ($r > 0.80$). As demonstrated in Figure IV-4 and IV-5, the Pearson correlation coefficient (r) was 0.985 ($p= 0.01$) for initial lymphedema volume and 0.987 ($p= 0.01$) for final lymphedema volume when comparing the calculated lymphedema volume from circumference measurements to water displacement lymphedema volume. The results demonstrated that the calculated lymphedema volume based on circumference measurement was highly correlated to, and thus a reliable predictor of, water displacement lymphedema volume. Using the same protocol, Karges et al., (1996) assessed the relationship between the two measurement methods in determining arm volume and reported a correlation of $r = 0.99$ from data on eight subjects (80). Megens et al., (2001) in a study of 25 breast cancer women at risk for lymphedema, reported an $r = 0.97$ for calculated arm volume from circumference measurements to water volume (83). The authors also examined the limits of agreement between the methods and concluded that, despite the high correlation, the two methods should not be used interchangeably.

The present study found a similar high association between the two methods when assessing initial and final lymphedema volume with data from 49 and 44 subjects respectively. Clinically, circumference measurements are simple, more efficient and feasible to use in any setting. Researchers and clinicians, if interested in the direction of change in lymphedema volume, could therefore choose either measurement method as long as the same measurement method was used consistently. As the limits of agreement between the methods were not analyzed in the present study, further study in the area is warranted.

VI: CHAPTER SIX

SUMMARY AND CONCLUSIONS

VI-1. SUMMARY:

The purpose of this study was to determine the efficacy of manual lymph drainage by comparing the reduction in arm lymphedema volume of subjects receiving manual lymph drainage in combination with multi-layered compression bandaging, to that achieved by subjects receiving multi-layered compression bandaging alone. The rate of reduction in lymphedema volume was analyzed to provide insight into the effect of the treatments over time. In addition, the association between lymphedema volume as determined by water volumetry to the volume calculated from circumference (girth) measurements was demonstrated.

Fifty subjects participated in the study, with twenty-five randomized to each group. All subjects were screened to ensure all inclusion and exclusion criteria were met prior to participating in the study. A total of 45 subjects completed the study, with 44 subjects evaluable for the primary outcome of lymphedema volume as determined from water displacement volumetry.

Appropriate descriptive statistics were used to characterize the subjects and inferential statistics were used to determine if any significant differences existed in the characteristics of subjects between the groups. Paired t-tests were performed to analyze the results of treatment within groups and independent t-tests were used to compare the results between groups. A two-way ANOVA repeated measurements analysis was used to assess the rate of reduction between the groups and for the exploratory analyses. Pearson product moment correlation tests were used to calculate the correlation between water displacement volumetry to the calculated volume determined from circumference measurements. All analyses employed the significance level of 0.05.

A significant reduction in lymphedema volume was found within each group, therefore the first and second hypotheses were accepted. The third hypothesis was rejected as no significant difference was found in the lymphedema volume reduction between the MLD/CB and CB groups. The fourth hypothesis was rejected, as no significant difference was found between the groups in the rate of lymphedema reduction over the four-week treatment period. The fifth hypothesis was accepted as a significantly high correlation was found between the two measuring techniques in determining lymphedema volume. Exploratory subgroup analyses demonstrated a significantly larger relative reduction in subjects with mild lymphedema that received MLD/CB when compared to all other subgroups.

VI-2. STUDY STRENGTHS:

The present study was a randomized controlled trial and to date, few randomized controlled treatment studies have been done specifically for breast cancer related lymphedema. The experimental model enhanced the internal validity of the study as extraneous factors were controlled, and as randomization of subjects reduced selection bias (76). The agreement to participate in the study was high (83%) and despite the lengthy treatment period and the requirement of constant bandaging, 45 subjects (90%) completed the study. The sample was also a representative sample of subjects normally seen in the clinical setting. The study design followed standard clinical treatment protocols for the duration of treatment whereas previous studies have shortened the treatment period. All research personnel were trained and experienced in the treatment method assigned. Independent assessors (IA) were used to administer the outcome measurements and were blinded to treatment allocation. The IA's were trained in the measurement protocols and the ICC's for both inter-rater and intra-rater reliability of the IA's exceeded the acceptable standard. The strengths of the study provide confidence that the results were due to treatment effects and not extraneous factors.

V-3. LIMITATIONS:

V-3-a. Sample Size

A larger sample would have detected smaller differences, and therefore, there is the potential that, due to the modest sample size, the findings of the present study findings reflect a Type II error (finding no significant difference when a difference really does exist). Moreover, a larger sample would have provided more confidence that randomization had adequately controlled for known and unknown confounding variables. The large ranges in both the initial volume, in the time from surgery and in the reported duration of lymphedema were not anticipated (Table IV-1). Casley-Smith (1995) in a consecutive series of patients with post mastectomy lymphedema (n = 231) found a significant increase in both the volume of lymphedema and in the degree of fibrosis in the arm, over time (16). Therefore, the severity of lymphedema and the subsequent treatment response may have been affected by the length of time the individual had endured lymphedema. As demonstrated in Table IV-5 and IV-6, however, there was no significant difference in the reduction achieved between the moderate and severe lymphedema subgroups in this study. To date, there is no clear method of assessing the function of the lymphatic system, therefore a larger sample would have allowed for further subgroup analyses and provided more confidence in the statistical conclusions. For the primary endpoint of the present study, though, a 20% difference in treatment response (effect size) between the groups was considered necessary to have clinical significance and to justify the costs associated with MLD application.

V-3-b. Measurement

The results were limited by the reliability of the Independent Assessor (IA) to measure the volume of lymphedema using the methods of volumetry and circumference measurements of the arm. To ensure accuracy of the measurements strict procedures were followed for both measurement methods (Appendix J and Appendix M). For water displacement volumetry, the starting level of water, the temperature of water, the position of the hand and limb were controlled to enhance the precision of the measurement. For instance, a time period of 20 seconds was observed from the time the water flow ceased (started to drip) from the outflow spout. This controlled time period allowed for the collection of the small amount of water that continued to drip from the outflow spout.

Though a longer time period may have resulted in a slightly more accurate measurement, it is extremely difficult for subjects to hold the position for longer than 20 seconds. Subjects, who had larger arms or were generally less mobile, had even more difficulty attaining and maintaining the required arm position for the water displacement volumetry. To avoid error, a second therapist was often required to assist in positioning and stabilizing the subject.

To minimize collecting and measurement errors, the displaced water was weighed rather than measured. Though there is a small error associated with the calculation of weight to volume, this error (overestimate of 5 mL per 1000 mL) was considered negligible given the potential errors (+/- 50 mL per 1000 mL) associated with measuring the volume in a graduated cylinder (83, 84).

The primary errors associated with measurement of circumference are due to differences in tension application of the tape measure and variations in measurement locations. These errors are of concern when more than one assessor is used (83). In the present study, the same IA was responsible for all the measurements for a given subject and the measurement locations were marked with indelible ink (Appendix M). In discussion with the independent assessors, there were other possible sources of error associated with the measurement of circumference. In some subjects, especially if a rapid reduction in lymphedema volume occurred, the skin became quite lax, and consistency in applying the appropriate tension to the tape measure was more difficult. As well, some subjects had difficulty maintaining the measuring marks (despite indelible ink) on the arm. This was more problematic on the unaffected side and when the weather was hot. (Anatomical landmarks such as the ulnar styloid were used, however, to improve accuracy of the measurement locations in the event that marks were removed.) As stated previously, an error was detected in the recorded measurement of the unaffected limb on initial assessment of one subject (subject 16). This error was detected by the IA-1 at the second measurement session and represented a recording error from the previous week.

The results of the measurement methods of volumetry and circumference measurement are limited to volume alone and do not account for changes in the composition of the tissues.

VI-4. CLINICAL SIGNIFICANCE:

Clinical significance is likely to vary depending on the volume of lymphedema. For instance, a 10% reduction in a subject with mild lymphedema may be insignificant clinically, whereas the same reduction in a severe edema may reduce pain and dramatically improve both function and cosmesis. Therefore, determining clinical significance will vary depending on the severity of, and symptoms associated with, the lymphedema. Though numerous classification systems have been developed (49, 79, 85), to date, no validated standards exist to classify lymphedema that would include objective analysis of lymphatic drainage in the limb, lymphedema volume and tissue fibrosis. Proposed classifications are based on volume alone and/ or subjective assessment of lymphedema stage. The effects of treatment on pain, range of motion, function and quality of life were not assessed in the present study and are essential components in determining clinical significance. Clearly multi-layered compression bandaging, with or without MLD, is an effective intervention in reducing arm lymphedema volume. Subjects with mild lymphedema would appear to benefit from the additional application of MLD; however, this finding will need to be further examined in the research setting. As demonstrated in this study, a variable response to treatment occurs therefore it is essential for physical therapists to evaluate the treatment they give.

VI-5. SUGGESTIONS FOR FUTURE RESEARCH:

This study has highlighted the need for several areas of future research and consideration:

1. There is a need to establish and validate a classification system for lymphedema based on the lymphedema volume, location of the lymphedema, and stage of tissue fibrosis, from which appropriate treatment may be determined.
2. Further study is needed examining validity and reliability of the measurement methods of water volumetry and the volume calculated from circumference measurements in determining lymphedema volume and in measuring change over time.
3. Future research directions should include determining the efficacy of other treatment components for lymphedema, such as exercise, prior to examining other combinations of treatment.
4. As lymphedema is a chronic condition, research into the durability of the treatment effect is needed and may involve examining adherence to use of compression sleeves and/or home maintenance programs.

5. Future studies should consider incorporating other outcome measurements in order to evaluate treatment effect on pain, range of motion, function and quality of life.

6. The efficacy of treatments, individually or in combination, will need to be evaluated for specific patient subsets, such as those with mild versus severe lymphedema, and those with early versus longstanding lymphedema.

VI-6. CONCLUSIONS:

As survival continues to improve for women with breast cancer, quality of life issues take on greater importance. Lymphedema is a progressive condition that can have profound adverse effects on the patient's quality of life, and is one of the most feared long-term complications of breast cancer treatment (86). As evidence-based medicine is now the foundation of the health care system, continuing research is needed to determine the efficacy of the various physical therapy methods used for the treatment of lymphedema. Policies and programming also reflect the overall strength of the available evidence and experimental studies provide the most convincing results. Currently in Canada, the primary treatments for lymphedema are compression pumps and compression sleeves. The findings of this study suggest that CB on its own should be considered as the primary treatment option in reducing arm lymphedema volume. The findings also suggest that efforts toward the treatment of lymphedema should be implemented as soon as possible after onset of the condition, when treatment is more likely to be effective.

Based on the findings of this study the following are recommended:

1. Given the greater probability that treatment will be more effective when initiated at a mild stage, efforts towards early detection and intervention are needed.
2. There is a need to establish and validate a classification system for lymphedema: based on volume/ location / stage from which appropriate treatment may be determined.
3. Further research is needed to examine appropriate outcome measures for determining treatment response. A reliable, valid and sensitive quality of life measure for breast cancer patients suffering from lymphedema is needed.
4. Multi-centre trials should be considered in order to obtain larger sample sizes and for accrual of subjects in a timely manner.

This study evaluated the efficacy of manual lymph drainage in women treated with multi-layered compression bandaging in the reduction of arm volume in breast cancer related lymphedema. Although the final overall average results did not attain statistical significance, the individual significance attained in some subjects with mild lymphedema indicates that MLD treatment may be warranted in selected situations.

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Appendix A

Vodder Method of Manual Lymph Drainage

VODDER METHOD OF MANUAL LYMPH DRAINAGE

Treatment Plan for Secondary Lymphedema of the Arm:

Supine Position

1. Neck lymph nodes:
    - Profundus to Terminus
    - Occiput to Terminus

2. Unaffected side of chest:
    - axillary lymph nodes
    - intercostals spaces
    - insertion of ribs on sternum

3. From the affected side of the chest over the vertical lymphatic watershed to the unaffected side:
    - windscreen wipers above the incision
    - rotary technique right and left of the incision
    - rotary technique from incision to inguinal area
    - insertion of ribs on sternum on the affected side

4. Lymphedema treatment of the arm
    - Thumb circles mid axilla to lateral arm, proximal to distal
    - pump-push on upper outer arm to terminus
    - large pump techniques over elbow to the terminus
    - spirals, medial to lateral over elbow crease
    - forearm edema technique
    - wrist, hand and finger treatment

5. From the affected side of the chest over the vertical lymphatic watershed to the unaffected side (repeat as in number 3 above).

Side Lying Position

1. Alternating rotary technique from the mid axillary line, over the spine to the affected side.

2. Intercostal spaces of the back, intensively with 8 fingers

3. Flat hand, stationary circles over the back extensor muscles.

4. Lay the arm of the affected side out straight and treat with pump-push to the shoulder, changing to rotary towards the back over the trapezius border.

Appendix B

Multi-layered Compression Bandaging

MULTI-LAYERED COMPRESSION BANDAGING

Materials

1. cotton tube stocking (stockinette)
2. elastic gauze for fingers
3. padding: foam or cotton batting (hand piece and roll for arm)
4. 3 to 4 short stretch tensor bandages (Comprilan) – one of each size: 4cm, 6 cm, 8cm (more may be required for larger arms)
5. Tape to fasten bandages (hockey tape)

Procedure

1. Apply stockinette to arm
2. Fingers: gently secure elastic gauze by wrapping one around the wrist. Each finger is then wrapped 3-4x without pulling on the gauze.
3. Apply partial padding to the back of the hand (hand piece) and secure with the remaining finger gauze.
4. Apply foam padding to the entire arm.
5. Wrap the arm with the smallest (4 cm) short-stretch tensor bandage (Comprilan) starting by securing the bandage at the wrist. The hand should be wrapped 3-4 times using the figure-of-eight method. Continue proximally up the arm, and overlap the first bandage by two-thirds. Tape should be applied to secure the end of the bandage. The second bandage (6 cm) should start proximal to the end of the first bandage. The overlap of the second and subsequent bandages should be one-half of the bandage width. The third bandage commences proximal to the end of the second bandage.

Bandaging Pressures in mmHg

	hand	forearm	elbow	upper arm
1	19	17	13	10
2	25	20	16	12
3	23	16	14	9
4	21	15	13	9
average	22	17	14	10

Appendix C

Student Project Research Review Committee

UNIVERSITY OF ALBERTA

September 15, 2000

Marjorie McNeely
Graduate Student
Department of Physical Therapy

Dear Marjorie:

Please accept my congratulations on approval of your proposal entitled the "Efficacy of Manual in reduction of arm volume in breast cancer related lymphdema". The committee was pleased with your preparation and proposal as its the defense. However there are some minor points which were pointed out to you during the meeting which I'm going to itemize. These should be used to modify the proposal before you send it to the Ethics Review Committee in the Faculty of Rehabilitation Medicine. The same modifications will be needed for the Ethics Review Committee of the Cross Cancer Hospital to inform them of the changes you have made. The suggestions are as follows:

1. Your committee desires that you should state your hypotheses in "if" and "so" format. This was explained to you during the meeting. If you are unclear about it please contact me.

2. You are suggested to test the validity of your volumeter as well as the reliability of the therapist by test and retest using a material which is known not to interfere with water update or water absorption. You should also indicate that you are making measurements and these are not necessarily measures of the "outcome".

3. You will also record the exercise regime which all your subjects may be on. Next you should provide a standard information to all your subjects who volunteer for this study. It is important that they receive identical information. It is therefore suggested that you develop a written package of the information which you will review with your subjects and give a copy to them. Next please extract information from the chart and enquire from the subjects of your study and information regarding medications as well as non medical supplements which they be on. Next you will give a clear and objective explanation of the discomfort for removing the bandage. Please also measure the tension in the bandage or the compression pressure which it applies to the surface of the skin and record it for each of the subject who you study.

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Hope these suggestions are helpful and clear to you. With these modifications your proposal will become a much stronger proposal.

Wish you success in your graduate endeavor and congratulations on clearing the SPERRC committee approval.

Yours sincerely,

SKumar

Shrawan Kumar, PhD, DSc, FErgS
Professor

cc Dr. David Magee
Student's File

Appendix D

Ethics Approval

LBERTA CANCER BOARD

andard Life Centre
220, 10405 Jasper Avenue
dmonton, AB T5J 3N4
anada

none: (780) 412-6300
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ERVING ALBERTANS
HROUGH THE
OLLOWING FACILITIES:

ross Cancer Institute
dmonton)

d its associate cancer centres:
Central Alberta Cancer Centre
(Red Deer)
Grande Prairie Cancer Centre

d its community cancer centres:
Aspen (Barrhead)
Bonnyville
Camrose
Northern Lights Regional Health
Services (Fort McMurray)
Hinton
Peace (Peace River)

om Baker Cancer Centre
Calgary)

nd its associate cancer centres:
Lethbridge Cancer Clinic
Medicine Hat Cancer Clinic

nd its community cancer centres:
Headwaters (High River)
Regional Health Authority #5
(Drumheller)

outhern Alberta Cancer
esearch Centre
Calgary)

creen Test:
he Alberta Program for the
arly Detection of Breast Cancer
ith clinics in Calgary and
dmonton and mobile units
rving rural Alberta

13 September 2000

OUR FILE: ETH-00-39-29
Please refer to the above number in all correspondence

Ms. Margie McNeely
Physical Therapist
Rehabilitation Department
Cross Cancer Institute

Dear Ms. McNeely:

Re: **The efficacy of manual lymphatic drainage in reduction of arm volume in breast cancer related lymphedema.**

On behalf of the Research Ethics Committee (REC), I have reviewed your revised consent form reflecting the recommended changes and the response to the concern the Committee had for the above-mentioned study.

I am pleased to inform you that scientific and ethical approval is granted for this protocol dated 27 August 2000, and the revised consent form, up to and including **13 September 2001.**

If there are any other changes to the protocol or consent form during the year, or if any adverse reactions to the treatment are found, the REC requests that you forward a letter describing the changes/reactions, per **CCI Policy 10A.16**, together with an updated consent form **to the Research Administration Office.**

Sincerely,

Sunil J. Desai, M.D.
Chair, Research Ethics Committee

/bee

cc: Edith Pituskin

Health Research Ethics Board biomedical research health research

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UNIVERSITY OF ALBERTA HEALTH SCIENCES FACULTIES,
CAPITAL HEALTH AUTHORITY, AND CARITAS HEALTH GROUP

HEALTH RESEARCH ETHICS APPROVAL

Date:	November 2000
Name of Applicant:	Ms. Margaret McNeely
Organization:	University of Alberta
Department:	Graduate Studies; Physical Therapy
Name of Supervisor:	Dr. David Magee
Organization:	University of Alberta
Department:	Physical Therapy
Project Title:	The Efficacy of Manual Lymph Drainage in the Reduction of Arm Volume in Breast Cancer Related Lymphedema

The Health Research Ethics Board has reviewed the protocol for this project and found it to be acceptable within the limitations of human experimentation. The HREB has also reviewed and approved the subject information material and consent form (if applicable).

The approval for the study as presented is valid for one year. It may be extended following completion of the yearly report form. Any proposed changes to the study must be submitted to the Health Research Ethics Board for approval.

Sharon Warren

Dr. Sharon Warren
Chair of the Health Research Ethics Board (B: Health Research)

File number: B-041000-REM

University of Alberta Capital Health CARITAS HEALTH GROUP

Appendix E

Information Letter and Pamphlet

INTRODUCTORY LETTER

Project Title: The efficacy of manual lymph drainage in the reduction of arm volume in breast cancer related lymphedema.

Investigators:
Mrs. Margie McNeely
Physical Therapist, Cross Cancer Institute
Dr. David Magee
Professor, University of Alberta
Dr. Alan Lees
Radiation Oncologist, Cross Cancer Institute

Dear ____________,

A research study is being done on arm swelling in breast cancer patients. This swelling is called lymphedema. Your physician has referred you to the physical therapy department for treatment of lymphedema. After this referral was received in our department, your physician was contacted and has consented that you be approached to take part in this study. Your participation in this study is entirely voluntary. You do not have to take part in this study and your care does not depend on whether you take part or not. Information on the study is provided on the enclosed pamphlet.

Your involvement in this study will be greatly appreciated, since results will teach us something about treating lymphedema. It is hoped that, in the long-term, patient care can be improved.

We will be calling you soon to ask whether you are willing to participate. If so, we will then arrange an interview session. If you have any questions before our call, please contact Margie McNeely, whose number is listed below. If you have any concerns about being contacted to participate in this study please call the Patient Advocate at (780) 432-8585.

Thank you for considering our request.

Sincerely,

____
Margie McNeely
Physical Therapist
Cross Cancer Institute
780-432-8716

THE EFFECT OF MANUAL LYMPH DRAINAGE MASSAGE ON ARM SWELLING IN BREAST CANCER PATIENTS

The purpose of this research is to examine the effect of a special form massage that has been developed to reduce arm swelling in breast cancer patients. This massage is called manual lymph drainage. The results of this work will help us to improve patient care for this condition.

Investigators involved in this study are Margie McNeely (Physical Therapist, Cross Cancer Institute), Dr. David Magee (Professor, Faculty of Rehabilitation Medicine) and Dr. Alan Lees (Radiation Oncologist, Cross Cancer Institute).

Each person enrolled in the study will be assigned to one of two groups. The groups will be decided by a process called "randomization". This means that the treatment is assigned by chance by a study coordinator at the Cross Cancer Institute.

If you get **Treatment "A"**, you will have to come to the Rehabilitation Department at the Cross Cancer Institute daily (Monday to Friday) for **4 weeks**. During these visits you will receive daily manual lymph drainage massage for 45 minutes. Following this your arm will be bandaged. You will be required to wear the bandages until your next treatment. Your treatment will take about one hour.

If you get **Treatment "B"**, you will have to come to the Rehabilitation Department at the Cross Cancer Institute daily (Monday to Friday) for **4 weeks**. During these visits your arm will be bandaged. You will be required to wear the bandages until your next treatment. Your treatment will take about 15 minutes.

Your arms will be measured at the beginning of the study and after each week of your treatment. **Measurements** will be taken along your arm using a tape measure. In order to measure the same spot each time small marks will be made on your arms with ink that is not easily washed off. Your **arm size** will also be measured **The** by having you place your arm in a warm **water tank**. The excess water will be collected and measured.

Feedback concerning the measures will be provided to you. Each measurement session will take 20 to 30 minutes to complete.

Your decision whether or not to participate in the study will in no way affect the other treatment or services you receive. Your physical therapist will discuss with you other treatment options available to patients with swelling in the arm.

Margie McNeely
Physical Therapist
Cross Cancer Institute 432-8716

Appendix F

Consent Form

THE EFFICACY OF MANUAL LYMPH DRAINAGE IN REDUCTION OF ARM VOLUME IN BREAST CANCER RELATED LYMPHEDEMA

(A STUDY TO FIND THE EFFECT OF MANUAL LYMPH DRAINAGE MASSAGE ON REDUCING ARM SWELLING IN BREAST CANCER PATIENTS)

Investigators: Mrs. Margie McNeely, Physical Therapist, Cross Cancer Institute phone: 432-8716
Dr. David Magee, Professor, University of Alberta phone: 492- 5765
Dr. Alan Lees, Radiation Oncologist, Cross Cancer Institute phone: 432-8518

CONSENT FORM

This consent form is part of the process of informed consent. It is designed to give you an idea of what this research study is about and what will happen to you if you choose to be in the study.

If you would like to know more about something mentioned in this form, or have any questions regarding this research study, please be sure to ask your physical therapist. Read this form carefully to make sure you understand all the information it provides. You will get a copy of this form to keep.

Your physician has consented that you be approached to take part in this study. Your participation in this study is entirely voluntary. You do not have to take part in this study and your care does not depend on whether you take part or not.

This study may not help you directly, but we hope that it will teach us something that will help others in the future.

BACKGROUND INFORMATION

Many breast cancer patients develop arm swelling after surgery and/or radiation therapy. This condition is known as lymphedema. There is no standard treatment for lymphedema. Treatment varies depending on where you live and depending on the knowledge of your healthcare provider. The best treatment or combination of treatments is not known. Complex Physical Therapy (CPT) is a combination of treatment techniques. This treatment program has been gaining popularity throughout North America. The main treatment in CPT is a massage technique called Manual Lymph Drainage (MLD).

Patient Initials ______________________________ Date ______________________________

CONSENT FORM

STUDY PURPOSE

The purpose of this study is to find out what effect the manual lymph drainage massage has on reducing the volume (size) of the arm. We will do this by comparing two different treatment groups.

STUDY DESIGN

If you choose to take part in this study, your treatment (A or B) will be decided by "randomization". This means your treatment will be assigned by chance by a study coordinator at the Cross Cancer Institute, Edmonton, Alberta. You have an equal chance of receiving either treatment. In this study one group will receive both massage and arm bandaging. The other group will receive arm bandaging only. You will be followed to see what effect the treatments have on the size of your arm.

Treatment A – Combined manual lymph drainage massage and multi-layered compression bandaging

If you get treatment A, you will have to come to the Rehabilitation Department at the Cross Cancer Institute daily (Monday to Friday) for four weeks. During these visits you will receive daily manual lymph drainage massage for 45 minutes. Following this your arm will be bandaged. It will take 10 minutes to bandage your arm. You will be required to wear the bandages until your next treatment, the following day. The total time for your appointment will be approximately one hour.

Treatment B- Multi-layered compression bandaging

If you get treatment B, you will have to come to the Rehabilitation Department at the Cross Cancer Institute daily (Monday to Friday) for four weeks. During these visits your arm will be bandaged. It will take 10 minutes to bandage your arm. You will be required to wear the bandages until your next treatment, the following day. The total time for your appointment will be approximately 15 minutes.

Patient Initials	Date
______________________	______________________

CONSENT FORM

INVESTIGATIONS DURING THE STUDY

All Treatments Groups

Your arms will be measured at the beginning of the study and after each week of your treatment. Measurements will be taken along your arm using a tape measure. In order to measure the same spot consistently, small marks will be made on your arms with ink that is not easily washed off. Your arm size will also be measured by having you place your arm in a warm water tank. The excess water will be collected and weighed. You will also be weighed, at this time, each week. It will take 20 to 30 minutes for all the measures to be taken.

ALTERNATIVE TREATMENTS

Your physical therapist will discuss with you other treatment options available to patients with lymphedema. Right now, the usual treatment is to receive a home program that includes daily bandaging of your arm, an exercise program and a self-massage program for your arm using a mechanical vibrator.

POTENTIAL BENEFITS

Past studies of both of these treatments have shown these techniques to decrease arm size. Participation in this study may be of no personal benefit to you. However, based on the results of this study, it is hoped that, in the long-term, patient care can be improved.

SIDE EFFECTS

The known side effect to the treatments is a small chance of skin allergy to the bandages. You should be made aware that the bandages that you will be required to wear on your arm, for four weeks, are bulky and may be cumbersome. You may find that this limits some of your normal activities.

If you have any side effects, you should call the physical therapist in charge of the study. The telephone numbers are on the last page of this form.

WITHDRAWAL FROM STUDY

In discussion with you, your doctor at the Cross Cancer Institute may withdraw you from the study at any time if it is in your best interests. You may also withdraw from the study at any time if you wish to do so.

Patient Initials ______________________ Date ______________________

CONSENT FORM

COSTS

You will not have to pay for the treatment you receive in this study. You will be coming to the Cross Cancer Institute more often than if you were not part of a study. There may be some extra costs, such as parking and meals, which you will have to pay.

CONFIDENTIALITY

All information will be held confidential except when professional codes of ethics and or legislation require reporting. The information that we collect as part of this study will be shared with other researchers and doctors. However, you will not be identified in any of these reports.

We will keep all the material we collect for this study in a safe storage area for a seven-year period. In the future, other researchers may want to use this material for new studies. Although we will not contact you if this happens, each new study will be reviewed to make sure that it is ethical.

UNDERSTANDING OF PARTICIPANTS

I am signing this form to show that I have read the consent form, and that I agree to take part in the study as a subject. In no way does this waive my legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities.

I can refuse to take part or withdraw from this study at any time without jeopardizing my health care. If I continue to take part in the study, I am to be kept as informed as my initial consent. I am free to ask for further explanations about this study. I understand that Margie McNeely (780) 432-8716 or (780) 432-8771 (CCI switchboard) will answer any questions I have about this study.

If I feel at any time that I have not been informed to my satisfaction about the risks, benefits, or alternatives of this study, or that I have been encouraged to continue in this study after I wanted to withdraw, I can call the Patient Advocate at (780) 432-8585.

I will get to keep a copy of this consent for information and for future reference.

(PRINT NAMES CLEARLY)

Name of Patient	Signature of Patient	Date & time
Name of Witness	Signature of Witness	
Name of Investigator	Signature of Investigator	

Appendix G

Sample Size

Sample Size

Table 4: Sample size calculations for treatment studies

1. Interval/ordinal dependent variable

$$\frac{n}{group} = \frac{2\sigma^2}{(\mu_2 - \mu_1)^2} \; x \; f\;(a,\beta)^1$$

where σ *= standard deviation for* $\mu 1$

μ_1 *= mean response on standard therapy*

} smallest difference if more than 2 Rx's

μ_2 *= mean response on comparison therapy*

Values of $f(\alpha, \beta)$ to be used in formula for required number of patients

		β (type II error)			
		0.05	0.1	0.2	0.5
α (type I error)	0.1	10.8	8.6	6.2	2.7
	0.05	13.0	10.5	7.9	3.8
	0.02	15.8	13.0	10.0	5.4
	0.01	17.8	14.9	11.7	6.6

Warren S. Statistical Analysis. In: Bartlett D. editor. Research Theory in Rehabilitation. Rehabilitation Research Centre, Faculty of Rehabilitation Medicine University of Alberta; 1994, p. 74

Sample Size Calculation

23% = standard deviation for usual treatment
20% = mean response on comparison therapy (MLD/CB) – mean response control group (CB)

alpha (a) = 0.05, beta (B) = 0.2

f (a,B) = 7.9

$$\text{n/group} = \frac{2\,(23^2)}{20^2} \times f\,(a, B)$$

$$= \frac{1058}{400} \times 7.9$$

$$= 2.645 \times 7.9$$

$$= 20.89$$

21 subjects are required per treatment group

Appendix H

Screening Chart

Screening Chart for Inclusion and Exclusion Criteria

Subject ID: **Name:**

Inclusion Criteria:

Sex: Female		**Yes**	No
A diagnosed breast cancer		**Yes**	No
Mono-lateral breast surgery		**Yes**	No
Axillary dissection		**Yes**	No
Diagnosis of lymphedema:	medical diagnosis	**Yes**	No
	150 ml volume of lymphedema	**Yes**	No
No active treatment for lymphedema in last 6 months		**Yes**	No
No new compression sleeve provided in last 4 months		**Yes**	No
Consent from subject's oncologist/surgeon/physician		**Yes**	No
Provide signed Informed Consent		**Yes**	No

Exclusion Criteria

Evidence of distant metastases or local recurrence		Yes	**No**
Radiotherapy or chemotherapy is currently being administered		Yes	**No**
Signs of infection:		Yes	**No**
Evidence of contraindications:	uncontrolled hypertension	Yes	**No**
	Heart disease	Yes	**No**
	Renal insufficiency	Yes	**No**
	Venous thrombosis	Yes	**No**

Qualification for this study	**Yes**	**No**

Appendix I

Subject Education

LYMPHEDEMA

What is lymph?

Lymph is a protein-rich fluid which gathers in the tissues. It is removed from the tissues by lymphatic channels which are similar to veins. The lymph fluid is then cleaned out in the lymph nodes, and it is returned to the blood.

What is lymphedema?

When the lymphatic system fails to remove the fluid from your tissues, swelling occurs. This swelling is known as lymphedema. It is most commonly seen in the arms or legs.

Why have I developed lymphedema?

Some people are born with a faulty lymphatic system. This is known as primary lymphedema.

Sometimes the lymphatic system is damaged (due to surgery, radiation therapy, blockage, infection or injury) and secondary lymphedema is the result. Most cancer patients have secondary lymphedema.

What can be done about my lymphedema?

At the present time, the damage to your lymphatic system cannot be repaired. However, your lymphedema can be reduced and controlled. Depending on your individual needs and reaction to treatment, the therapist will design a treatment program for you.

This may include some or all of the following:
- education
- compression pump treatments
- manual lymph drainage massage
- bandaging
- compression garments
- compression systems such as Reid Sleeve/Legacy system
- specialized exercises
- skin hygiene
- home massage program

Why do I need to worry about infection?

The lymphatic system has several functions. One function is to collect lymph (fluid) from the tissues and then return it to the blood. A second function is to filter or clean this fluid. This is done at the lymph node. If lymph is not being collected and cleaned at its normal rate it can become a breeding ground for bacteria. If bacteria enter your arm an infection may develop. An infection may cause your arm to look red, more swollen, and feel hot. You may also develop a fever and feel generally unwell.

The following are our guidelines for preventing inflammation and infection in the arm and hand:

1) **Avoid cuts, scratches, and irritation**
   - use rubber gloves for washing dishes
   - wear heavy gloves and long sleeves when gardening
   - wear a thimble when sewing
   - use an electric razor to remove hair from the armpit (keep your razor properly maintained)
   - avoid deodorants, soaps or lotions that cause skin irritation. A low pH lotion is recommended for cleansing the arm
   - do not use tanning dyes on your arm
   - when manicuring your nails, avoid cutting your cuticles (inform your manicurist)
2) **Do not have injections**
   - vaccinations or blood drawn on the affected arm (side of your breast cancer).

   Your other arm should be used. If your breast cancer is on both sides then an alternate site should be used: i.e. ankle area. If an arm must be used, then your wrist or the back of your hand are recommended.

3) **Avoid wasps, bees and other biting insects**
   - use insect repellent and/or wear long sleeves to protect against insect bites
   - use caution when traveling to other areas; i.e. Hawaii, tropical countries, far North

4) **Avoid burns and frostbite**
   - use an extra long padded glove when reaching into a hot oven
   - use protective sun lotion when in the sun or cover your arm with long sleeves or a towel
   - wear gloves or mittens when the weather is cold
   - keep the water temperature for baths and showers warm, not hot

5) **Avoid anything binding on your arm or chest wall**
- do not allow blood pressure to be taken on the affected side
- wear only loose jewelry, watches and clothing on the affected arm
- do not carry a heavy purse or bag over your shoulder on the affected side
- make sure that your brassiere does not dig into your shoulder (no indentations at top of shoulder) and that it is not tight around the chest wall

6) **Avoid straining or injuring your arm**
- no heavy lifting; i.e. furniture
- avoid repetitive lifting or repetitive movements against resistance; i.e. pushing, pulling, scrubbing, or carrying boxes when moving
- avoid activities that involve long periods with the arms down; i.e. knitting, vacuuming, driving long distances
- do not overtire your arm; if it starts to ache, lie down and elevate your arm

**ASK YOUR THERAPIST ABOUT
RETURNING TO
EXERCISE AND ACTIVITY**

7) **Take care of problems immediately**

In the case of scratches, hangnails, burns, etc.; keep area clean, apply a topical antibiotic (i.e. polysporin) and cover with a bandaid.

How do I know if I have an infection?

Watch for the following signs of inflammation or infection:

- warmth
- redness or red streaks (often on inside of forearm)
- rash
- sudden onset or increase in swelling
- pain (if severe)

What should I do if I think I have an infection?

See your doctor immediately. Your doctor may prescribe antibiotic medication for you.

**An infection may progress to acute illness (systemic infection)
with fever, weakness, aching, etc.
(This may require intravenous antibiotics - Report to a
Medical Centre or Emergency Department)**

Appendix J

Water Displacement Volumetry Procedures

PROCEDURES FOR WATER DISPLACEMENT

Equipment : volumeter, beaker for overflow of water, container for collecting arm overflow, thermometer, weigh scale, towels.

1. Mark the subject's limb at the elbow crease. Measure 16 cm proximal to the crease and mark the arm using indelible ink.
2. Fill the volumeter with warm water (30-34 degrees Celsius) until water overflows into beaker. Allow water flow to cease.
3. Position the collecting container to catch the displaced water.
4. Have the subject slowly immerse the limb. The arm must remain in the center of the volumeter and contact with the sides of the volumeter must be avoided. The subject continues to lower the arm into the water until the 16 cm mark is aligned with the lower portion of the outflow spout. A second therapist may be needed to assist in positioning and stabilizing the subject.
5. Allow the overflow to cease. A timed period of 20 seconds will be observed from the time the flow starts to cease (at a rate of one drip per second).
6. Weigh the collecting container with the overflow. (Subtract the weight of the container)
7. Based on: density of water = 1.0, 1 gram = 1 cubic centimetre = 1 millilitre.

Water is most dense @ 4 degrees celcius. Change in volume = (expansion coefficient) x starting volume x temp. So the volume of 1 cc would increase by .00546 cc going from 4 degrees to 30 degrees (84).

Appendix K

Data Collection Sheet for Volumetry and Body Weight

VOLUMETRIC MEASURES OF ARMS

Patient name: ____________________________
Patient code: ______________
Affected arm: right ___ left ____

	initial right arm	initial left arm	week 1 right arm	week 1 left arm	week 2 right arm	week 2 left arm	week 3 right arm	week 3 left arm	final right arm	final left arm
A: weight of water displaced										
B: weight of container										
A-B (weight)										
Volume										
Lymphedema volume*	xxxxx		xxxxx		xxxxx		xxxxx		xxxxx	
Change in milliliters**	xxxxx	xxxxx	xxxxx		xxxxx		xxxxx		xxxxx	
% lymphedema reduction***	xxxxx	xxxxx	xxxxx		xxxxx		xxxxx		xxxxx	
subject's weight (kg)		xxxxx		xxxxx		xxxxx		xxxxxx		xxxxx

*** lymphedema volume as expressed in milliliters = volume of affected arm – volume of unaffected arm**

****change in milliliters = initial lymphedema volume – current lymphedema volume**

*****% lymphedema reduction =**

$$\frac{\text{initial lymphedema volume (mls)} - \text{current lymphedema volume (mls)}}{\text{initial lymphedema volume (mls)}} \times 100$$

Appendix L

Formula for a Truncated Cone

Volumetric Calculation

Variation of mathematical formula for truncated cone:

$V = (h)\ (C^2 + Cc + c^2)\ /\ 12\ (\pi)$

where: **h = perpendicular height of the segment**

C = top of the cone

c = bottom of the cone

$\pi = 3.1416$

(Karges, 1996)

Appendix M

Procedures for Circumference Measurements

PROCEDURES FOR LIMB MEASUREMENT USING CIRCUMFERENCE MEASUREMENTS

Tools: Tape measure (Fibreglass, nonstretch), Indelible ink pen, Wedge, Metre stick

Procedures:

1. Position the subject in sitting with the hand supported on the wedge, shoulder in 90 degrees abduction. (If position cannot be achieved, an alternate position with the arm in 45 degrees flexion will be used. The measurement position will be recorded.)
2. Calibrate the tape measure with the metre stick to ensure that it has not stretched.
3. Mark the limb with indelible ink:

- start by marking distal to the ulnar styloid
- mark the distance from the distal end of the little finger to the ulnar styloid for future reference
- mark the distal aspect of the fifth MCP, record the distance
- mark the just distal to the widest part of the hand including the thumb, record the distance
- mark the limb every 4 cm, adjust the measurements to include the crease of the elbow, record the distance from the last forearm mark to the mark of the elbow crease
- continue every 4 cm above the elbow crease to the axilla

4. Measure the circumference as marked above.

   -Place the tape measure so that its top edge is just below the appropriate mark.

   - the tape should lie flat without indenting the skin
   - ensure that the tape is perpendicular to the arm

5. Record the circumferences on the collection sheet.

Appendix N

Data Collection Sheet: Circumferential Measures

DATA COLLECTION SHEET FOR CIRCUMFERENTIAL MEASURES

Patient name:________________________
Patient code: __________
Affected arm: Right_____ **Left** ______

	Height	Initial	Initial	Week 1	Week 1	Week 2	Week 2	Week 3	Week 3	Final	Final
		Right	Left	R	L	R	L	R	L	R	L
MCP											
hand with thumb MCP											
wrist*_____											
4 cm	4										
8 cm	4										
12 cm	4										
16 cm	4										
20 cm	4										
24 cm	4										
28 cm	4										
Elbow (from last measure= _____cm)											
4 cm above elbow	4										
8 cm	4										
12 cm	4										
16 cm	4										
20 cm	4										
volume**											

*** a measure will be taken from the distal end of the little finger to the wrist mark and recorded.**

**** volume will calculated using the following formula:**

$V = (h)\ (C^2 + Cc + c^2) / 12\ (3.14)$

h = height
C = circumference at top of cone
c = circumference at bottom of cone

Appendix O

Script for Clerical Staff

Script for Clerical Staff

Form: to be attached to referral by physical therapist screening the referrals

Patient name: ______________________________
Cross Cancer ID: __________________ Referring physician: ___________
Patient Phone number: ___________

Questions:

Patient is eligible for study? ______ (yes/no) _______(initials of therapist)

If eligible, referring physician has provided consent to approach patient? _____(yes/no) ______ (PI, initials). If yes, continue with the following instructions.

Follow normal phone procedures for booking appointments and provide the following additional information about the study. Please place a check mark following each sentence.

1. We would also like to let you know that a research study is being done on arm swelling in breast cancer patients. ____

2. The purpose of this study is to determine the effect of a special form of massage that has been developed to reduce arm swelling in breast cancer patients. ___

3. The principal investigator of the study is one of our physical therapists, Margie McNeely. ____

4. The study is being done in our physical therapy department, here at the Cross Cancer Institute. Your physician, _______________, has consented that you be approached to take part in this study ___

5. If you feel that you may be interested in taking part in the study, we will mail you a letter and pamphlet that provides information about the study. ___

6. Margie (clarify who she is, if necessary) will then call you soon after to ask whether you are willing to participate. If so, Margie will then arrange an interview session to discuss the details about the study. ___

7. We would like you to know that you do not have to take part in this study and that your care does not depend on whether you take part or not. ___

Do you feel that you would like us to send you information about taking part in this study?
____ If yes, letter and pamphlet sent _____________(date)

Whether you decide to participate or not:
You do have an appointment booked for ___________________ (date and time), with ______________(physical therapist) for an assessment of your arm swelling.

_____________________ _____________________ _____________
print name of clerical staff *date* *initials*

Appendix P

Data Collection Sheet: Demographics

DATA COLLECTION SHEET: DEMOGRAPHICS

Patient Name: ____________________________

Patient code: _________________

Age: _________ **DOB:** ____________

Type of breast cancer: _____________ **Stage of breast cancer:** ________________

Date of Surgery: _____________________ **Type of Surgery:** __________________

Post-operative infection: yes or no

Chemotherapy: type _____________

Radiation: _____________

Date of onset of Lymphedema: _______________

Arm involved: R or L **Dominant arm:** R or L

Medications: ____

____

Vitamins: ____

Appendix Q

Pilot Reliability Data

Validity testing of the Volumeter:

1. Measurement of water added in and water displaced out.

	Volume In	Volume Out	Difference
1	500 mL	495 mL	5 mL
2	1000 mL	995 mL	5 mL
3	1500 mL	1490 mL	10 mL
4	2000 mL	1990 mL	10 mL
5	3000 mL	3000 mL	0 mL
Total	8000 mL	7970 mL	30 mL (99.6%)

A small amount of water added in was lost during the process. A loss in water output was anticipated and likely due to a small amount of water remaining in the input container and clinging to the overflow spout of the volumeter (as the time period from end of flow was timed for a 20 second period). The mean error of measurement was 0.4%.

2. Measurement of replicated limb (water added to a surgical glove or veterinary plastic arm sleeve).

	Estimated Volume In	Measured Volume Out	Difference
1	310 mL	310 mL	0 mL
2	505 mL	495 mL	10 mL
3	845 mL	830 mL	15 mL
4	1500 mL	1480 mL	20 mL
5	3000 mL	2965 mL	35 mL
Total	6160 mL	6080 mL	80 mL (98.7%)

A small amount of water was lost, as above. As well, some accuracy was likely lost due to difficulty aligning the pliable water filled sleeve to the level of the outflow spout of the volumeter. The mean error of measurement was 1.3%.

Pilot Reliability Study: Water Displacement Volumetry

Intra-rater reliability IA -1

Subject	Measure 1 (mL)	Measure 2 (mL)	Measure 3 (mL)
1	3465	3465	3370
2	2615	2615	2615
3	3175	3165	3165
4	3230	3180	3155
5	3240	3195	3205
6	2145	2145	2165
7	2195	2210	2225
8	2510	2430	2530
9	1585	1600	1580
10	1585	1550	1570
11	3080	3080	3070
12	2020	1970	1990

Correlation = r = 0.998-0.999

Kendall's Tau_b: correlation coefficient = 0.962-0.992

$$\text{ICC }(3,k) = \frac{\text{BMS - EMS}}{\text{BMS}} = \frac{417210-192}{417210} = 0.99$$

(76)

Pilot Reliability: Calculated Volume Circumference Measurements

Intra-rater reliability: IA-1

Subject	Measure 1 (mL)	Measure 2 (mL)	Measure 3 (mL)
1	3389	3407	3446
2	2704	2775	2807
3	3470	3425	3423
4	3493	3520	3529
5	2945	2922	2933
6	2097	2073	2063
7	2006	2005	2002
8	2368	2385	2374
9	1669	1658	1657
10	1626	1622	1612
11	3160	3151	3132
12	2170	2158	2173

Correlation = $r = 0.998 - 0.999$

Kendall's Tau_b: correlation coefficient = 0.998 - 1.00

$$ICC\,(3,k) = \frac{BMS - EMS}{BMS} = \frac{479948 - 203}{479948} = 0.9995$$

(76)

Intra-rater reliability

IA-2

Water Displacement

Subject	Measure 1 (mL)	Measure 2 (mL)	Measure 3 (mL)
1	1800	1850	1800
2	2275	2245	2225
3	2800	2815	2790
4	2425	2395	2375
5	2650	2550	2660
6	2500	2510	2480

Calculated Volume

1	2101	2107	2123
2	3080	3067	3057
3	2599	2563	2556
4	2900	2890	2874
5	3073	3065	3049
6	3601	3592	3557

Water Volumetry:

Correlation = r = 0.988 - 0.997
Kendall's Tau_b: correlation coefficient = 0.998 - 1.00

$$\text{ICC }(3,k) = \frac{\text{BMS - EMS}}{\text{BMS}} = \frac{124044 - 143}{124044} = 0.998$$

Circumference Measurements:

Correlation = r = 0.999 - 1.00
Kendall's Tau_b: correlation coefficient = 1.00

$$\text{ICC} = \frac{253939 - 207}{253939} = 0.999$$

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